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JC662 U.S. PTO 10/13/99

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	8535-027-999	*Total Pages*	197
First Named Inventor or Application Identifier			
Michael Nehls			
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JC672 U.S. PTO 09/417502 10/13/99

APPLICATION ELEMENTS
See MPEP chapter 600 concerning utility patent application contents.

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1. ☒ Fee Transmittal Form
   Submit an original, and a duplicate for fee processing)
2. ☒ Specification [*Total Pages* 84]
   (preferred arrangement set forth below)
   - -Descriptive title of the Invention
   - -Cross Reference to Related Applications
   - -Statement Regarding Fed sponsored R&D
   - -Reference to Microfiche Appendix
   - -Background of the Invention
   - -Brief Summary of the Invention
   - -Brief Description of the Drawings *(if filed)*
   - -Detailed Description of the Invention (including drawings, *if filed*)
   - -Claim(s)
   - -Abstract of the Disclosure
3. ☒ Drawing(s) *(35 USC 113)* [*Total Sheets* 1]
4. ☒ Oath or Declaration (unexecuted) [*Total Sheets* 2]
   a. ☐ Newly executed (original or copy)
   b. ☐ Copy from a prior application (37 CFR 1.63(d))
   (for continuation/divisional with Box 17 completed)
   [Note Box 5 below]
   i. ☐ DELETION OF INVENTOR(S)
   Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33 (b).
5. ☐ Incorporation By Reference *(useable if Box 4b is checked)*
   The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
6. ☐ Microfiche Computer Program *(Appendix)*
7. ☒ Nucleotide and/or Amino Acid Sequence Submission
   (if applicable, all necessary)
   a. ☐ Computer Readable Copy
   b. ☒ Paper Copy (109 pages)
   c. ☐ Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

8. ☐ Assignment Papers (cover sheet & document(s))
9. ☐ 37 CFR 3.73(b) Statement ☐ Power of Attorney
   (when there is an assignee)
10. ☐ English Translation Document *(if applicable)*
11. ☐ Information Disclosure Statement (IDS)/PTO-1449 ☐ Copies of IDS Citations
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17. **If a CONTINUING APPLICATION,** *check appropriate box and supply the requisite information:*
☐ Continuation ☐ Divisional ☒ Continuation-in-part (CIP) of prior application No: 60/104,292 filed 10/14/98.

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NOVEL HUMAN POLYNUCLEOTIDES AND THE POLYPEPTIDES ENCODED THEREBY

This application claims priority to United States Provisional Application No. 60/104,292, filed October 14, 1998, which is also incorporated herein by reference for any purpose.

1. FIELD OF THE INVENTION

The present invention is in the field of molecular genetics. The application discloses novel nucleic acid sequences that partially define the scope of human exons that can be trapped and identified by the disclosed vectors/methods, and which are useful, *inter alia*, for identifying the organization of the coding regions and of the human genome.

2. BACKGROUND OF THE INVENTION

The Human Genome Project and privately financed ventures are currently sequencing the human genome, and the substantial completion of this milestone is expected before the year 2003. The hope is that, at the conclusion of the sequencing phase, a comprehensive representation of the human genome will be available for biomedical analysis. However, the data resulting from such efforts will largely comprise human genomic sequence of which only a fraction actually encodes expressed sequence information. Although sophisticated computer-assisted exon identification programs can be applied to such genomic sequence data, the computer predictions require verification by laboratory analysis to actually identify the coding regions of the genome. Consequently, the availability of cDNA information will significantly contribute to the value of the human genomic sequence since cDNA sequence provides a direct indication of the presence of transcribed sequences as well as the location of splice junctions. Thus, the sequencing of cDNA libraries to obtain expressed sequence tags (or ESTs) that identify exons expressed within a given tissue, cell, or cell line is currently in progress. As a consequence of these efforts, a large number of EST sequences are presently compiled in public and privately held databases. However, the present EST paradigm is inherently limited by the levels and extent of mRNA production within a given cell. A related problem is the lack of cDNA sources from specific tissue and developmental

expression profiles. In addition, some genes are typically only active under certain physiological conditions or are generally expressed at levels below or near the threshold necessary for cDNA cloning and detection and are therefore not effectively represented in current cDNA libraries.

Researchers have partially addressed these issues by using phage vectors to clone genomic sequences such that internal exons are trapped (Nehls, *et al.*, 1994, Current Biology, *4(1)*:983-989, and Nehls, *et al.*, 1994, Oncogene, *9*:2169-2175). However, such libraries require the random cloning of genomic DNA into a suitable cloning vector *in vitro*, followed by reintroduction of the cloned DNA *in vivo* in order to express and splice the cloned genes prior to producing the cDNA library. Additionally, such methods can only "trap" the internal exons of genes. Consequently, genes containing a single exon or a single intron are typically not trapped by traditional methods of exon trapping.

3. SUMMARY OF THE INVENTION

The subject invention provides numerous isolated and purified novel human cDNAs produced using gene trap technology. The novel human gene trapped sequences (GTSs) of the subject invention are disclosed as SEQ ID NOS:9-503 in the appended Sequence Listing.

The subject invention further contemplates the use of one or more of the subject GTSs, or portions thereof, to isolate cDNAs, genomic clones, or full-length genes/polynucleotides, or homologs, heterologs, paralogs, or orthologs thereof, that are capable of hybridizing to one or more of the disclosed GTSs or their complementary sequences under stringent conditions.

The subject invention additionally contemplates methods of analyzing biopolymer (*e.g.*, oligonucleotides, polynucleotides, oligopeptides, peptides, polypeptides, proteins, etc.) sequence information comprising the steps of loading a first biopolymer sequence into or onto an electronic data storage medium (*e.g.*, digital or analogue versions of electronic, magnetic, or optical memory, and the like) and comparing said first sequence to at least a portion of one of the polynucleotide sequences, or amino acid sequence encoded thereby, that is first disclosed in, or otherwise unique to, SEQ ID NOS:9-503. Typically, the polynucleotide sequences, or amino acid sequences encoded thereby, will also be present on,

or loaded into or onto a form of electronic data storage medium, or transferred therefrom, concurrent with or prior to comparison with the first polynucleotide.

Another embodiment of the invention is the use of a oligonucleotide or polynucleotide sequence first disclosed in at least a portion of at least one of the GTS sequences of SEQ ID NOS:9-503 as a hybridization probe. Of particular interest is the use of such sequences in conjunction with a solid support matrix/substrate (resins, beads, membranes, plastics, polymers, metal or metallized substrates, crystalline or polycrystalline substrates, etc.). Of particular note are spatially addressable arrays (*i.e.*, gene chips, microtiter plates, etc.) of polynucleotides wherein at least one of the polynucleotides on the spatially addressable array comprises an oligonucleotide or polynucleotide sequence first disclosed in at least one of the GTS sequences of SEQ ID NOS:9-503.

Similarly, one or more oligonucleotide probes based on, or otherwise incorporating, sequences first disclosed in any one of SEQ ID NOS:9-503, can be used in methods of obtaining novel gene sequence via the polymerase chain reaction or by cycle sequencing. Similar oligonucleotide hybridization probes can also comprise sequence that is complementary to a portion of a sequence that is first disclosed in, or preferably unique to, at least one of the GTS polynucleotides in the sequence listing. The oligonucleotide probes will generally comprise between about 8 nucleotides and about 80 nucleotides, preferably between about 15 and about 40 nucleotides, and more preferably between about 20 and about 35 nucleotides.

Moreover, an oligonucleotide or polynucleotide sequence first disclosed in at least one of the GTS sequences of SEQ ID NOS:9-503 can be incorporated into a phage display system that can be used to screen for proteins, or other ligands, that are capable of binding an amino acid sequence encoded by an oligonucleotide or polynucleotide sequence first disclosed in at least one of the GTS sequences of SEQ ID NOS:9-503.

An additional embodiment of the present invention is a library comprising individually isolated linear DNA molecules corresponding to at least a portion of the described human GTSs which are useful for synthesizing physically contiguous sequences of overlapping GTSs by, for example, the polymerase chain reaction (PCR).

The subject invention also provides for an antisense molecule which comprises at least a portion of sequence that is first disclosed in, or preferably unique to, at least one of the GTS polynucleotides.

The subject invention also contemplates a purified polypeptide in which at least a portion of the polypeptide is encoded by, and thus first disclosed by, at least a portion of a GTS of the present invention. The invention also relates to naturally occurring polynucleotides comprising the disclosed GTSs that are expressed by promoter elements other than the promoter elements that normally express the GTSs in human cells (*i.e.*, gene activated GTSs). Such promoter elements can be directly incorporated into the cellular genome or recombinantly engineered upstream from at least a portion of a GTS (preferably at least about 50, more preferably at least about 75, and most preferably at least about 100 to 130 base in length) of the present invention, or a complement thereof. A particularly preferred embodiment includes recombinantly engineered expression vectors that similarly have or incorporate at least a, preferably unique, portion of the disclosed GTSs or complement thereof.

4. DESCRIPTION OF THE SEQUENCE LISTING AND FIGURES

The Sequence Listing is a compilation of nucleotide sequences obtained by sequencing a human gene trap library that at least partially identifies the genes in the target cell genome that can be trapped by the described gene trap vectors (*i.e.*, the repertoire of genes that are active or have not been inactivated).

Figures 1A-1D. Figure 1A illustrates a retroviral vector that can be used to practice the described invention. Figure 1B shows a schematic of how a typical cellular genomic locus is effected by the integration of the retroviral construct into intronic sequences of the cellular gene. Figure 1C shows the chimeric transcripts produced by the gene trap event as well as the locations of the binding sites for PCR primers. Figure 1D shows how the PCR amplified cDNAs are directionally cloned into a suitable GTS vector.

5. DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to novel human polynucleotide sequences obtained from cDNA libraries generated by the normalized expression of genomic exons using gene trap technology. In particular, the disclosed novel polynucleotides were generated using a modified reverse-orientation retroviral gene trap vector that was nonspecifically integrated into the target cell genome, although other polynucleotide (DNA or RNA) gene trap vectors could have been introduced to the target cells by, for example, transfection, electroporation, or retrotransposition. Preferred retroviral vectors that can be used to practice the present invention (as well as methods and recombinant tools for making and using the described GTSs) are disclosed in, *inter alia*, U.S. Application Ser. No. 09/276,533, filed March 25, 1999 which is herein incorporated by reference in its entirety.

After integration, the exogenous promoter of the sequence acquisition, or 3' gene trap, component of the vector was used to express and splice a chimeric mRNA that was subsequently reverse transcribed, amplified, and subject to DNA sequence analysis. Unlike conventional cDNA libraries, the presently disclosed libraries are largely unaffected by the bias inherent in cDNA libraries that rely solely on endogenous mRNA expression. Additionally, by integrating a vector into the target cell genes, a chimeric mRNA is produced that allows for the specific expansion and isolation of cDNAs corresponding to the chimeric mRNAs using vector specific primers.

As used herein the term "gene trapped sequence", or "GTS", refers to nucleotide sequences that correspond to naturally occurring endogenously encoded human exons that have been expressed as part of a chimeric "gene trapped" mRNA. Typically, the chimeric mRNA incorporates at least a portion of sequence that has been engineered into the sequence acquisition exon of a gene trap vector which, *inter alia*, facilitates cDNA production by reverse transcriptase and amplification of the cDNA by PCR to produce an isolated linear DNA molecule. The disclosed GTSs do not include vector encoded sequences.

The term "GTS" not only refers to polynucleotides that are exactly complementary to naturally occurring human mRNA, but also refers to "GTS derivatives". The term "GTS derivative" also refers to heterologs, paralogs, orthologs, and allelic variants of the specific

GTSs described herein. In addition, a GTS may include the complete coding region for a naturally occurring peptide or polypeptide. A GTS may also include a complete open reading frame.

The term "GTS peptide" as used herein includes oligopeptides or polypeptides sharing biological activity and/or immunogenicity (or immunological cross-reactivity) with an amino acid sequence encoded by at least one of the disclosed GTSs or complement thereof. The terms "biological activity" (or "biological characteristics") of a polypeptide refers to the structural or biochemical function of the polypeptide in the normal biological processes of the organism in which the polypeptide naturally occurs. Examples of such characteristics include protein structure and/or conformation, which can be determined biochemically by reaction with appropriate ligands or receptors or by suitable biological assays.

A GTS peptide may also correspond to a full-length naturally occurring peptide or polypeptide. GTS peptides can have amino acid sequences that directly correspond to naturally occurring polypeptides or amino acid sequences or can comprise minor variations. Such variations can include amino acid substitutions that are the result of the replacement of one amino acid with another amino acid having a similar structural and/or chemical properties, such as the substitution of a leucine with an isoleucine or valine, an aspartate with a glutamate, or a threonine with a serine, *i.e.*, conservative amino acid replacements. Additional variations include minor amino acid deletions and/or insertions, typically in the range of about 1 to 6 amino acids, and can also include one or more amino acid substitutions. Guidance in determining which GTS peptide amino acid residues can be replaced or deleted without abolishing the biological activity of interest may be determined empirically, or by using computer amino acid sequence databases to identify polypeptides that are homologous to a given GTS peptide and trying to avoid amino acid substitutions in conserved regions of homology.

"Homology" refers to the similarity or the degree of similarity between a reference, or known polynucleotide and/or polypeptide and a test nucleotide sequence and/or its corresponding amino acid sequence. As used herein, "homology" is defined by sequence similarity between a reference sequence and at least a portion of the newly sequenced

nucleotide. Typically, a corresponding amino acid sequence similarity should exist between the peptides encoded by such homologous sequences.

To determine whether proteins are homologous, the GTS sequence is translated into the corresponding amino acid sequence. The amino acid sequence is then compared with reference polypeptide sequences. A short string of matching amino acid sequence can constitute good evidence of homology (for example, repeating Gly-Pro-X sequence, or the presence of an RGD motif). However, typically a larger number of similar amino acids is required to label two sequences homologous. Generally, the match needs to be at least about 7 or 8 amino acids, among which perhaps one mismatch is allowed. These criteria allow good sensitivity in finding all relevant sequences while providing a threshold amount of selectivity.

After peptide homology has been found, the respective nucleotide sequences are compared. An alignment of the reference and new sequences should show at least about 60%, and preferably at least about 65%, agreement over the minimum of 21 nucleotides which correspond to the 6 matching amino acids. Generally, a low percentage of agreement is acceptable if the differences are in the "wobble" position (or third nucleotide of the triplet coding for an amino acid).

As used herein, a "mutated" polypeptide has an altered primary structure typically resulting from corresponding mutations in the nucleotide sequence encoding the protein or polypeptide. As such, the term "mutated" polypeptides can include allelic variants. Mutational changes in the primary structure of a polypeptide result from deletions, additions or substitutions. A "deletion" is defined as a change in a polypeptide sequence in which one or more internal amino acid residues are absent. An "addition" is defined as a change in a polypeptide sequence which has resulted in one or more additional internal amino acid residues as compared to the wild type. A "substitution" results from the replacement of one or more amino acid residues by other residues. A polypeptide "fragment" is a polypeptide consisting of a primary amino acid sequence which is identical to a portion of the primary sequence of the polypeptide to which the polypeptide is related.

A host cell "expresses" a gene or DNA when the gene or DNA is transcribed into RNA that may optionally be translated to produce a polypeptide.

The subject invention also includes GTSs which are incorporated into expression vectors and transformed into host cells which subsequently express the polynucleotides and/or polypeptides encoded by the GTSs.

The subject invention also includes antibodies capable of specifically binding to GTS peptides, as well as methods of detecting a GTS peptides or the corresponding protein by combining a sample for analysis with an antibody capable of specifically binding to a GTS peptide and detecting the formation of antibody complexes present in the sample.

The subject invention also includes a method of isolating a GTS peptide, or its corresponding protein comprising the step of separating the GTS peptide, or its corresponding protein, from a solution utilizing an antibody capable of specifically binding to the GTS peptide or its corresponding protein.

The subject invention also provides for markers for use in detecting diseases, biological events, cell types and tissues which comprise at least a portion of a GTS sequence.

Further, the subject invention provides polynucleotide markers useful for physical and genetic mapping of the human, and/or certain model organism, genome(s). In particular, the nucleotide sequences in the Sequence Listing provide sequence tagged sites (STS), that will be useful in completing an STS-based physical map of the human genome, a goal of the human genome project (Collins, F. and Galas, D. (1993) Science *262*:43-46). Additionally, some of these sequences will identify new genes. These new genes will be useful in completing physical and genetic maps of all the genes in the human genome, another goal of the human genome project.

The exons contained in the disclosed GTSs contain open reading frames (present in one of the three reading frames in either orientation of the sequence). Typically, the gene trap strategy employed to generate the GTS sequences allows for the directional cloning and identification of the sense strand. However, it is possible that occasional sequencing errors or random reverse transcription, or PCR aberrations will mask the presence of the appropriate open reading frame. In such cases of sequencing error, it is possible to determine the corresponding GTS sequence by expressing the GTS in an appropriate expression system and determining the amino acid sequence by standard peptide mapping and sequencing techniques (Current Protocols in Molecular Biology, John Wiley & Sons, Vol. 2, Sec 16,

1989). Additionally, the actual reading frame and amino acid sequence of a given nucleotide sequence may be determined by *in vitro* synthesis of a portion of an oligopeptide comprising a possible amino acid sequence and preparing antibodies to the oligopeptide. If the antibodies react with cells from which the GTS of interest was derived, the reading frame is likely correct. Alternatively, codon usage analysis can be used to track and correct reading frame shifts in gene sequence data.

The correct amino acid sequence of a GTS protein is largely a function of the DNA sequence and the correct amino acid sequence can be readily determined using routine techniques. For example, by providing independent three fold sequencing coverage of the GTS library, random sequencing/RT/PCR errors can be identified and corrected by selecting the sequence represented by the majority of gene trap sequences covering a given nucleotide.

The nucleotide sequences of the Sequence Listing may contain some sequencing errors and several of the nucleotide sequences of the Sequence Listing may contain nucleotides that have not been precisely identified, typically designated by an N, rather than A, T, C, or G. Since each of the nucleotide sequences presented in the Sequence Listing is believed to uniquely identify a novel GTS, any sequencing errors or N's in the nucleotide sequences of the Sequence Listing do not present a problem in practicing the subject invention. Several methods employing standard recombinant methodology, for example, as described in Molecular Cloning: Laboratory Manual 2nd ed., Sambrook *et al.* (1989), Cold Spring Harbor Laboratory, Cold Spring Harbor, NY (or periodic updates thereof), may be used to correct errors and complete the missing sequence information. For example, a nucleotide and/or oligonucleotide corresponding to a portion of a nucleotide sequence of GTS of interest, can be chemically or biochemically synthesized *in vitro,* and used as a hybridization probe to screen a cDNA library in order to identify and obtain library isolates comprising recombinant DNA sequences containing the GTS cDNA sequence of interest. The library isolate may then be independently subjected to nucleotide sequencing using one or more standard sequencing procedures so as to obtain a complete and accurate nucleotide sequence.

For the purposes of this disclosure, the term "isolated and purified polynucleotide" comprises a polynucleotide purified from a natural cell or tissue as well as polynucleotides

which are complementary to the polynucleotides isolated from the natural cell or tissue. One example of an isolated or purified polynucleotide, or a substantially isolated preparation thereof, is a preparation where the polynucleotide of interest represents at least about 80 percent, preferably at least about 85 percent, and more preferably at least about 90 to 95 percent or more of the net product(s) that can be visualized on a DNA agarose gel stained with ethidium bromide.

The described GTSs were obtained from isolates of a cDNA library. Clones isolated from cDNA libraries generated by 3' gene trapping typically contain only a portion of the mature RNA transcript that has been spliced to a vector encoded sequence acquisition exon, and therefore such clones may only encode a portion of the polypeptide of interest (however, it should be appreciated that a number of the disclosed GTSs may encode full- length ORFs). To obtain the remainder of the sequence, the GTSs can be used as hybridization probes to re-screen the same or a different cDNA library, and additional clones isolated by the re-screening can be purified and characterized using standard methods (Benton and Davis, 1977, Science, *196*:180-183). Once sufficiently purified, the size of the DNA insert can be approximated by agarose gel electrophoresis and the larger clones can be analyzed to determine the exact number of bases by DNA sequencing. Frequently, the use of a library different from the one which contained the original clone is useful for this purpose, and particularly a library that has been prepared with extra care to extend cDNA synthesis to full-length, or a library that has been intentionally primed with random primers in order to "jump over" particularly difficult regions of the transcript sequence.

Missing upstream DNA sequence can also be obtained by "primer extension" of the cDNA isolate, a practice common in the art (Sambrook *et al.* (1989), Molecular Cloning: Laboratory Manual 2nd ed. pg 7.79-7.83, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY), whereby a sequence-specific oligonucleotide is used to prime reverse-transcription near the 5'-end of the cDNA clone and the resulting product is either cloned into a bacterial vector or is analyzed directly by DNA sequencing. Finally, newer methods to extend clones in either direction employ oligonucleotide-directed thermocyclic DNA amplification of the missing sequences, wherein a combination of a cDNA-specific primer and a degenerate, vector-specific, or oligo-dT-binding second oligonucleotide can be used to

prime strand synthesis. In any of the above methods or other methods of detecting additional cDNA sequence, two or more resulting clones containing the partial cDNA sequence can be recombined to form a single full-length cDNA by standard cloning methods. The resulting full-length cDNA may subsequently be transferred into any of a number of appropriate expression vectors.

In many instances, the sequencing of clones resulting from independent nonspecific gene trap events will result in a natural redundancy of sequencing more than one cDNA from a particular gene. As discussed above, this feature is a built in form of error detection and correction. These independent gene trap events can also be combined using the various overlapping regions of sequence into an entire contiguous sequence ("contig") containing the complete nucleotide sequence of the full length cDNA. Similar methodology can be used to combine one or more GTSs with one or more publicly available, or proprietary, ESTs to synthesize, electronically or chemically, a contiguous sequence.

The ABI Assembler application, part of the INHERITS DNA analysis system (Applied Biosystems, Inc., Foster City, CA), creates and manages sequence assembly projects by assembling data from selected sequence fragments into a larger sequence. The Assembler combines two advanced computer technologies which maximize the ability to assemble sequenced DNA fragments into Assemblages, a special grouping of data where the relationships between sequences are shown by graphic overlap, alignment and statistical views. The process is based on the Meyers-Kececioglu model of fragment assembly (INHERITS™ Assembler User's Manual, Applied Biosystems, Inc., Foster City, CA), and uses graph theory as the foundation of a very rigorous multiple sequence alignment program for assembling DNA sequence fragments. Additional methods of using GTSs and obtaining full length versions thereof are discussed in U.S. Patent No. 5,817,479, herein incorporated by reference.

It will be appreciated by those skilled in the art that as a result of the degeneracy of the genetic code (see, for example, Table 4-1 at page 109 of "Molecular Cell Biology", 1986, J. Darnell *et al.* eds., Scientific American Books, New York, NY, herein incorporated by reference) a multitude of GTS nucleotide sequences, some bearing minimal nucleotide sequence homology to the nucleotide sequence of genes naturally encoding GTS peptides,

can be produced. The invention has specifically contemplated each and every possible variation of nucleotide sequence that could be made by selecting combinations based on possible codon choices. These combinations are made in accordance with the standard triplet genetic code as applied to the nucleotide sequence of naturally occurring human GTS nucleotide sequences and all such variations are to be considered as being specifically disclosed. Once the triplet codons are "translated" (which can be done electronically) into their amino acid counterparts, the amino acid sequences encoded by the GTS ORFs effectively represent a generic representation of the various nucleotide sequences that can encode the amino acid sequence (*i.e.*, each amino acid is generic for the various nucleotide codons that correspond to that amino acid).

The presently described novel human GTSs provide unique tools for diagnostic gene expression analysis, for cross species hybridization analysis, for genetic manipulations using a variety of techniques, like, for example, antisense inhibition, gene targeting, the identification or generation of full-length cDNA, mapping exons in the human genome, identifying exon splice junctions, gene therapy, gene delivery, chromosome mapping, etc. Furthermore, the expression-based detection and isolation of the described novel polynucleotides verifies that the genes encoding these sequences have not been inactivated by, for example, the covalent modification (methylation, acetylation, glycosylation, etc.) of the target cell genome, or inhibiting the function of transcriptional control elements. The fact that the genes have not been inactivated in the target cell genome can indicate an involvement in cellular metabolism, catabolism, homeostasis, or any of a wide variety of developmental and cell differentiation processes or the regulation of physiological or endocrine functions in the body, etc. (although treating the target cell with, for example, histone deacetylators can partially compensate for such inactivation and expand the target size of a given trapping construct). These data are especially useful when correlated with cDNA data from differentiated tissues and/or cells or cell lines in order to determine whether the absence of expression is regulated at the level of transcription or gene inactivation.

5.1 POLYNUCLEOTIDES OF THE PRESENT INVENTION

The nucleotide sequences of the various isolated human GTSs of the present invention appear in the Sequence Listing as SEQ ID NOS:9-503. Additional embodiments of the present invention are GTS variants, or homologs, paralogs, orthologs, etc., which include isolated polynucleotides, or complements thereof, that hybridize to one or more of the disclosed GTSs of SEQ ID NOS:9-503 under stringent, or preferably highly stringent, conditions. By way of example and not limitation, high stringency hybridization conditions can be defined as follows: Prehybridization of filters containing DNA to be screened is carried out for 8 h to overnight at 65°C in a buffer containing 6X SSC, 50mM Tris-HCl (pH 7.5), 1mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.02% BSA, and 500 μg/ml denatured salmon sperm DNA. Filters are hybridized for 48 h at 65°C in prehybridization mixture containing 100μg/ml denatured salmon sperm DNA and 5-20 x 10^6 cpm of ^{32}P-labeled probe (alternatively, as in all hybridizations described herein, approximately 42, 44, 46, 48, 50, 52, 54, 56, 58, 62, 64, 66, 68, 70, or about 72 degrees or more can be used). The filters are then washed in approximately 1X wash mix (10X wash mix contains 3M NaCl, 0.6M Tris base, and 0.02M EDTA, alternatively, as with all washes described herein, 2X, 3X, 4X, 5X, 6X wash mix, or more, can be used) twice for 5 minutes each at room temperature, then in 1X wash mix containing 1% SDS at 60°C (alternatively, as in all washes described herein, approximately 42, 44, 46, 48, 50, 52, 54, 56, 58, 62, 64, 66, 68, 70, or about 72 degrees or more can be used) for about 30 min, and finally in 0.3X wash mix (alternatively, as in all final washes described herein, approximately, 0.2X, 0.4X, 0.6X, 0.8X, 1X, or any concentration between about 2X and about 6X can be used in conjunction with a suitable wash temperature) containing 0.1% SDS at 60°C (alternatively, approximately 42, 44, 46, 48, 50, 52, 54, 56, 58, 62, 64, 66, 68, 70, or about 72 degrees or more can be used) for about 30 min. The filters are then air dried and exposed to x-ray film for autoradiography. In an alternative protocol, washing of filters is done at 37°C for 1 h in a solution containing 2X SSC, 0.01% PVP, 0.01% Ficoll, and 0.01% BSA. This is followed by a wash in 0.1X SSC at 50°C for 45 min before autoradiography. Another example of hybridization under highly stringent conditions is hybridization to filter-bound DNA in 0.5 M $NaHPO_4$, 7% sodium dodecyl sulfate (SDS), 1 mM EDTA at 65°C, and washing in 0.1xSSC/0.1% SDS at 68°C

(Ausubel F.M. *et al.*, eds., 1989, Current Protocols in Molecular Biology, Vol. I, Green Publishing Associates, Inc., and John Wiley & sons, Inc., New York, at p. 2.10.3).

Preferably, such GTS variants will encode at least a portion or domain of a, preferably naturally occurring, protein or polypeptide that encodes a functional equivalent to a protein or polypeptide, or portion or domain thereof, encoded by the disclosed GTSs. Additional examples of GTS variants include polynucleotides, or complements thereof, that are capable of binding to the disclosed GTSs under less stringent conditions, such as moderately stringent conditions, (*e.g.*, washing in 0.2xSSC/0.1% SDS at 42° C (Ausubel *et al.*, 1989, *supra*). Moderately stringent conditions can be additionally defined, for example, as follows: Filters containing DNA are pretreated for 6 h at 55°C in a solution containing 6X SSC, 5X Denhart's solution, 0.5% SDS and 100 μg/ml denatured salmon sperm DNA. Hybridizations are carried out in the same solution and 5-20 x 10^6 cpm ^{32}P-labeled probe is used. Filters are incubated in hybridization mixture for 18-20 h at 55°C (alternatively, as in all hybridizations described herein, approximately 42, 44, 46, 48, 50, 52, 54, 56, 58, 62, 64, 66, 68, 70, or about 72 degrees or more can be used in combination with a suitable concentration of salt). The filters are then washed in approximately 1X wash mix (10X wash mix contains 3M NaCl, 0.6M Tris base, and 0.02M EDTA, alternatively, as with all washes described herein, 2X, 3X, 4X, 5X, 6X wash mix, or more, can be used) twice for 5 minutes each at room temperature, then in 1X wash mix containing 1% SDS at 60°C (alternatively, as in all washes described herein, approximately, 42, 44, 46, 48, 50, 52, 54, 56, 58, 62, 64, 66, 68, 70, or about 72 degrees or more can be used) for about 30 min, and finally in 0.3X wash mix (alternatively, as in all final washes described herein approximately 0.2X, 0.4X, 0.6X, 0.8X, 1X, or any concentration between about 2X and about 6X can be used in conjunction with a suitable wash temperature) containing 0.1% SDS at 60°C (alternatively, approximately 42, 44, 45, 48, 50, 52, 54, 56, 58, 62, 64, 66, 68, 70, or about 72 degrees or more can be used) for about 30 min. The filters are then air dried and exposed to x-ray film for autoradiography.

In an alternative protocol, washing of filters is done twice for 30 minutes at 60°C in a solution containing 1X SSC and 0.1% SDS. Filters are blotted dry and exposed for autoradiography.

Other conditions of moderate stringency which may be used are well-known in the art.

For example, washing of filters can be done at 37°C for 1 h in a solution containing 2X SSC, 0.1% SDS. Another example of hybridization under moderately stringent conditions is washing in 0.2xSSC/0.1% SDS at 42°C (Ausubel et al., 1989, *supra).* Such less stringent conditions may also be, for example, low stringency hybridization conditions. By way of example and not limitation, procedures using such conditions of low stringency are as follows (see also Shilo and Weinberg, 1981, Proc. Natl. Acad. Sci. USA 78:6789-6792): Filters containing DNA are pretreated for 6 h at 40°C in a solution containing 35% formamide, 5X SSC, 50mM Tris-HCl (pH 7.5), 5mM EDTA, 0.1% PVP, 0.1% Ficoll, 1% BSA, and 500 μg/ml denatured salmon sperm DNA. Hybridizations are carried out in the same solution with the following modifications: 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100μg/ml salmon sperm DNA, 10% (wt/vol) dextran sulfate, and 5-20 X 10^6 cpm ^{32}P-labeled probe is used. Filters are incubated in hybridization mixture for 18-20 h at 40°C (alternatively, as in all hybridizations described herein, approximately 42, 44, 46, 48, 50, 52, 54, 56, 58, 62, 64, 66, 68, 70, or about 72 degrees or more can be used). The filters are then washed in approximately 1X wash mix (10x wash mix contains 3M NaCl, 0.6M Tris base, and 0.02M EDTA, alternatively, as with all washes described herein, 2X, 3X, 4X, 5X, 6X wash mix, or more, can be used) twice for five minutes each at room temperature, then in 1X wash mix containing 1% SDS at 60°C (alternatively, as in all washes described herein, approximately 42, 44, 46, 48, 50, 52, 54, 56, 58, 62, 64, 66, 68, 70, or about 72 degrees or more can be used) for about 30 min, and finally in 0.3X wash mix (alternatively, as in all final washes described herein, approximately, 0.2X, 0.4X, 0.6X, 0.8X, 1X, or any concentration between about 2X and about 6X can be used in conjunction with a suitable wash temperature) containing 0.1% SDS at 60°C (alternatively, approximately 42, 44, 46, 48, 50, 52, 54, 56, 58, 62, 64, 66, 68, 70, or about 72 degrees or more can be used) for about 30 min. The filters are then air dried and exposed to x-ray film for autoradiography. In yet another alternative protocol, washing of filters is done for 1.5 h at 55°C in a solution containing 2X SSC, 25mM Tris-HCl (pH 7.4), 5mM EDTA, and 0.1% SDS. The wash solution is replaced with fresh solution and incubated an additional 1.5 h at 60°C. Filters are then blotted dry and exposed for autoradiography. If necessary, filters are washed for a third time at 65-68°C and reexposed to film. Other conditions of low stringency which may be used are well known in the art (*e.g.*,

as employed for cross-species hybridizations). Preferably, GTS variants identified or isolated using the above methods will also encode a functionally equivalent gene product (*i.e.*, protein, polypeptide, or domain thereof, encoding or otherwise associated with a function or structure at least partially encoded by the complementary GTS).

Additional embodiments contemplated by the present invention include any polynucleotide sequence comprising a continuous stretch of nucleotide sequence originally disclosed in, or otherwise unique to, any of the GTSs of SEQ ID NOS:9-503 that are at least 8, or at least 10, or at least 14, or at least 20, or at least 30, or at least about 40, and preferably at least about 60 consecutive nucleotides up to about several hundred bases of nucleotide sequence or an entire GTS sequence. Functional equivalents of the gene products of SEQ ID NOS:9-503 include naturally occurring variants of SEQ ID NOS:9-503 present in other species, and mutant variants, both naturally occurring and engineered, which retain at least some of the functional activities of the gene products of SEQ ID NOS:9-503.

The invention also includes degenerate variants of the claimed GTS sequences, and products encoded thereby. Such variants may be 80% identical to any one of SEQ ID NOS: 9-503, more preferably 85%, more preferably 90%, more preferably 95% and most preferably 98% identical. The degree of identity (or the degree of homology) of a polynucleotide sequence to any one of SEQ ID NOS: 9-503 may be determined using any sequence analysis program known in the art, for example, the University of Wisconsin GCG sequence analysis package, SEQUENCHER 3.0, Gene Codes Corp., Ann Arbor, MI. The invention further includes GTS derivatives wherein any of the disclosed GTSs, or GTS variants, is linked to another polynucleotide molecule, or a fragment thereof, wherein the link may be either directly or through other polynucleotides of any sequence and of a length of about 1,000 base pairs, or about 500 base pairs, or about 300 base pairs, or about 200 base pairs, or about 150 base pairs, or about 100 base pairs or about 50 base pairs, or less.

The invention also particularly includes polynucleotide molecules, including DNA, that hybridize to, and are therefore the complements of, the nucleotide sequences of the disclosed GTSs. Such hybridization conditions may be highly stringent or less highly stringent, as described above. In instances wherein the nucleic acid molecules are deoxyoligonucleotides ("DNA oligos"), highly stringent conditions may refer to, for example,

washing in 6xSSC/0.05% sodium pyrophosphate at 37° C (for oligos having 14-base DNA oligos), 48° C (for 17-base DNA oligos), 55° C (for 20-base DNA oligos), and 60°C (for 23-base oligos). Similar conditions are contemplated for RNA oligos corresponding to a portion of the disclosed GTS sequences.

These nucleic acid molecules may encode or act as antisense molecules to polynucleotides comprising at least a portion of the sequences shown in SEQ ID NOS:9-503 that are useful, for example, to regulate the expression of genes comprising a nucleotide sequence of any of SEQ ID NOS:9-503, and can also be used, for example, as antisense primers in amplification reactions of gene sequences. With respect to gene regulation, such techniques can be used to regulate, for example, developmental processes by modulating the expression of genes in embryonic stem cells. Further, such sequences may be used as part of ribozyme and/or triple helix sequences that can be used to regulate gene expression. Still further, such molecules may be used as components of diagnostic methods whereby, for example, the presence of a particular allele, of a gene that contains any of the sequences of SEQ ID NOS:9-503 may be detected. Of particular interest is the use of the disclosed GTSs to conduct analysis of single nucleotide polymorphisms (SNPs), and particularly coding region SNPs or "cSNPs", in the human genome, or as general or individual-specific forensic markers. When so applied, a collection of GTSs is obtained from an individual, and screened against a control database of cSNPs (or other genetic markers) that have previously been associated with disease, suitability or susceptibility (or sensitivity) to specific drugs or therapies, or virtually any other human trait that correlates with a given cSNP or genetic marker, or assortment thereof. In addition to disease/diagnostic testing, the described GTSs are also useful as genetic markers for the prenatal analysis of congenital traits or defects.

In addition to the nucleotide sequences described above, full length cDNA or gene sequences that contain any of SEQ ID NOS:9-503 present in the same species and/or homologs of any of those genes present in other species can be identified and isolated by using molecular biological techniques known in the art.

In order to clone the full length cDNA sequence from any species encoding the cDNA corresponding to the entire messenger RNA or to clone variant or heterologous forms of the molecule, labeled DNA probes made from nucleic acid fragments corresponding to any of the

partial cDNA disclosed herein may be used to screen a cDNA library. For example, oligonucleotides corresponding to either the 5' or 3' terminus of the cDNA sequence may be used to obtain longer nucleotide sequences. Briefly, the library may be plated out to yield a maximum of about 30,000 pfu for each 150 mm plate. Approximately 40 plates may be screened. The plates are incubated at 37° C until the plaques reach a diameter of 0.25 mm or are just beginning to make contact with one another (3-8 hours). Nylon filters are placed onto the soft top agarose and after 60 seconds, the filters are peeled off and floated on a DNA denaturing solution consisting of 0.4N sodium hydroxide. The filters are then immersed in neutralizing solution consisting of 1 M Tris HCl, pH 7.5, before being allowed to air dry. The filters are prehybridized in casein hybridization buffer containing 10% dextran sulfate, 0.5 M NaCl, 50 mM Tris HCL, pH 7.5, 0.1% sodium pyrophosphate, 1% casein, 1% SDS, and denatured salmon sperm DNA at 0.5 mg/ml for 6 hours at 60° C. The radiolabelled probe is then denatured by heating to 95° C for 2 minutes and then added to the prehybridization solution containing the filters. The filters are hybridized at 60° C (alternatively, as in all hybridizations described herein, approximately 42, 44, 46, 48, 50. 52, 54, 56, 58, 62, 64, 66, 68, 70, or about 72 degrees or more can be used) for about 16 hours. The filters are then washed in approximately 1X wash mix (10X wash mix contains 3M NaCl, 0.6M Tris base, and 0.02M EDTA, alternatively, as with all washes described herein, 2X, 3X, 4X, 5X, 6X wash mix, or more, can be used) twice for 5 minutes each at room temperature, then in 1X wash mix containing 1% SDS at 60° C (alternatively, as in all washes described herein, approximately 42, 44, 46, 48, 50. 52, 54, 56, 58, 62, 64, 66, 68, 70, or about 72 degrees or more can be used) for about 30 min, and finally in 0.3X wash mix (alternatively, as in all final washes described herein, approximately, 0.2X, 0.4X, 0.6X, 0.8X, 1X, or any concentration between about 2X and about 6X can be used in conjunction with a suitable wash temperature) containing 0.1% SDS at 60° C (alternatively, approximately 42, 44, 46, 48, 50. 52, 54, 56, 58, 62, 64, 66, 68, 70, or about 72 degrees or more can be used) for about 30 min. The filters are then air dried and exposed to x-ray film for autoradiography. After developing, the film is aligned with the filters to select a positive plaque. If a single, isolated positive plaque cannot be obtained, the agar plug containing the plaques will be removed and placed in lambda dilution buffer containing 0.1M NaCl, 0.01M magnesium

sulfate, 0.035M Tris HCl, pH 7.5, 0.01% gelatin. The phage may then be replated and rescreened to obtain single, well isolated positive plaques. Positive plaques may be isolated and the cDNA clones sequenced using primers based on the known cDNA sequence. This step may be repeated until a full length cDNA is obtained.

It may be necessary to screen multiple cDNA libraries from different sources/tissues to obtain a full length cDNA. In the event that it is difficult to identify cDNA clones encoding the complete 5' terminal coding region, an often encountered situation in cDNA cloning, the RACE (Rapid Amplification of cDNA Ends) technique may be used. RACE is a proven PCR-based strategy for amplifying the 5' end of incomplete cDNAs. 5'-RACE-Ready cDNA synthesized from human fetal liver containing a unique anchor sequence is commercially available (Clontech). To obtain the 5' end of the cDNA, PCR is carried out, for example, on 5'-RACE-Ready cDNA using the provided anchor primer and the 3' primer. A secondary PCR reaction is then carried out using the anchored primer and a nested 3' primer according to the manufacturer's instructions.

Once obtained, the full length cDNA sequence may be translated into amino acid sequence and examined for certain landmarks found in the amino acid sequences encoded by SEQ ID NOS:9-503, or any structural similarities to these disclosed sequences.

The identification of homologs, heterologs, or paralogs of SEQ ID NOS:9-503 in other, preferably related, species can be useful for developing additional animal model systems that are closely related to humans for purposes of drug discovery. Genes at other genetic loci within the genome that encode proteins which have extensive homology to one or more domains of the gene products encoded by SEQ ID NOS:9-503 can also be identified via similar techniques. In the case of cDNA libraries, such screening techniques can identify clones derived from alternatively spliced transcripts in the same or different species.

Screening can be done using filter hybridization with duplicate filters. The labeled probe can contain at least 15-30 base pairs of the nucleotide sequence presented in SEQ ID NOS:9-503. The hybridization washing conditions used should be of a lower stringency when the cDNA library is derived from an organism different from, or heterologous to, the type of organism from which the labeled sequence was derived. With respect to the cloning of a mammalian homolog, heterolog, ortholog, or paralog, using probes derived from any of

the sequences of SEQ ID NOS:9-503, for example, hybridization can, for example, be performed at 65° C overnight in Church's buffer (7% SDS, 250 mM $NaHPO_4$, 2 mM EDTA, 1% BSA). Washes can be done with 2XSSC, 0.1% SDS at 65° C and then at 0.1XSSC, 0.1% SDS at 65° C.

Low stringency conditions are well known to those of skill in the art, and will vary predictably depending on the specific organisms from which the library and the labeled sequences are derived. For guidance regarding such conditions see, for example, Sambrook *et al.*, 1989, Molecular Cloning, A Laboratory Manual, Cold Springs Harbor Press, N.Y.; and Ausubel *et al.*, 1989, Current Protocols in Molecular Biology, Green Publishing Associates and Wiley Interscience, N.Y.

Alternatively, the labeled nucleotide probe of a sequence of any of SEQ ID NOS:9-503 may be used to screen a genomic library derived from the organism of interest, again, using appropriately stringent conditions. The identification and characterization of human genomic clones is helpful for designing diagnostic tests and clinical protocols for treating disorders in human patients that are known or suspected to be linked to disease or other developmental or cell differentiation disorders and abnormalities. For example, sequences derived from regions adjacent to the intron/exon boundaries of the human gene can be used to design primers for use in amplification assays to detect mutations within the exons, introns, splice sites (*e.g.*, splice acceptor and/or donor sites), etc., that can be used in diagnostics.

Further, gene homologs can also be isolated from nucleic acid of the organism of interest by performing PCR using two oligonucleotide primers derived from SEQ ID NOS:9-503 or two degenerate oligonucleotide primer pools designed on the basis of amino acid sequences within the gene products encoded by SEQ ID NOS:9-503. The template for the reaction may be cDNA obtained by reverse transcription of mRNA prepared from, for example, human or non-human cell lines, cell types, or tissues, like, for example, ES cells from the organism of interest.

The PCR product may be subcloned or sequenced directly or subcloned and sequenced to ensure that the amplified sequences represent the sequences of the gene corresponding to the sequence of SEQ ID NOS:9-503 of interest. The PCR fragment may then be used to isolate a full length cDNA clone by a variety of methods. For example, the

amplified fragment may be labeled and used to screen a cDNA library, such as a bacteriophage cDNA library. Alternatively, the labeled fragment may be used to isolate genomic clones via the screening of a genomic library.

PCR technology may also be utilized to isolate full length cDNA sequences. For example, RNA can be isolated using standard procedures from an appropriate cellular source (*i.e.*, one known, or suspected, to express the gene corresponding to the sequence of SEQ ID NOS:9-503 of interest, such as, for example, ES cells). A reverse transcription reaction may be performed on the RNA using an oligonucleotide primer specific for the most 5' end of the amplified fragment for the priming of first strand synthesis. The resulting RNA/DNA hybrid may then be "tailed" with guanines, for example, using a standard terminal transferase reaction, the hybrid may be digested with RNase H, and second strand synthesis may then be primed with a poly-C primer. Thus, cDNA sequences upstream from the amplified fragment may easily be isolated. For a review of cloning strategies which may be used, see *e.g.*, Sambrook *et al.*, 1989, supra. Alternatively, cDNA or genomic libraries can be screened using 5' PCR primers that hybridize to vector sequences and 3' PCR primers specific to the gene of interest. Typically, such primers comprise oligonucleotide "priming" sequences first disclosed in, or otherwise unique to, one of the GTSs of SEQ ID NOS:9-503.

The sequence of a gene corresponding to any of the sequences of SEQ ID NOS:9-503 can also be used to isolate mutant alleles of that gene. Such mutant alleles may be isolated from individuals either known or suspected to have a genotype which contributes to the disease of interest or other symptoms of developmental and cell differentiation and/or proliferation disorders and abnormalities. Mutant alleles and mutant allele products may then be utilized in the therapeutic and diagnostic programs described below. Additionally, such sequences of any of the genes corresponding to SEQ ID NOS:9-503 can be used to detect gene regulatory (*e.g.*, promoter or promoter/enchancer) defects which can affect development or cell differentiation.

A cDNA of a mutant gene corresponding to any of the sequences of SEQ ID NOS:9-503 can be isolated as discussed above, or, for example, by using PCR. In this case, the first cDNA strand may be synthesized by hybridizing an oligo-dT oligonucleotide to mRNA isolated from cells derived from an individual suspected of carrying a mutant gene

corresponding to any of the sequences of SEQ ID NOS:9-503 by extending the new strand with reverse transcriptase. The second strand of the cDNA is then synthesized using an oligonucleotide that hybridizes specifically to the 5' region of the normal gene. The amplified product can be directly sequenced or cloned into a suitable vector and subsequently subjected to DNA sequence analysis. By comparing the DNA sequence of the mutant allele to that of the normal allele, the mutation(s) responsible for the loss or alteration of function of the mutant gene product can be ascertained.

Alternatively, a genomic library can be constructed using DNA obtained from one or more individuals suspected of carrying, or known to carry, a mutant allele corresponding to any of SEQ ID NOS:9-503. Corresponding mutant cDNA libraries can be also constructed using RNA from cell types known, or suspected, to express such mutant alleles. The corresponding normal gene, or any suitable fragment thereof, may then be labeled and used as a probe to identify the corresponding mutant allele in such libraries. Clones containing the mutant gene sequences may then be identified and analyzed by DNA sequence analysis. Additionally, a protein expression library can be constructed utilizing cDNA synthesized from, for example, RNA isolated from a cell type known, or suspected, to express a mutant allele corresponding to any of the sequences of SEQ ID NOS:9-503 from an individual suspected of, carrying or known to carry, such a mutant allele. In this manner, gene products made by the putatively mutant cell type may be expressed and screened using standard antibody screening techniques in conjunction with antibodies raised against the corresponding normal gene product or a portion thereof, as described below in Section 5.4 (For screening techniques, see, for example, Harlow, E. and Lane, eds., 1988, "Antibodies: A Laboratory Manual", Cold Spring Harbor Press, Cold Spring Harbor.) Additionally, screening can be accomplished by screening with labeled fusion proteins. In cases where a mutation results in an expressed gene product with altered function (*e.g.*, as a result of a missense or a frame shift mutation), a polyclonal set of antibodies to the wild-type gene product are likely to cross-react with the mutant gene product. Library clones detected via their reaction with such labeled antibodies can be purified and subjected to sequence analysis according to methods well known to those of skill in the art.

The invention also encompasses nucleotide sequences that encode mutant isoforms of any of the amino acid sequences encoded by the GTSs of SEQ ID NOS:9-503, peptide fragments thereof, truncated versions thereof, and fusion proteins including any of the above. Examples of such fusion proteins can include, but not limited to, an epitope tag which aids in purification or detection of the resulting fusion protein; or an enzyme, fluorescent protein, luminescent protein which can be used as a marker.

The present invention additionally encompasses (a) RNA or DNA vectors that contain any portion of SEQ ID NOS:9-503 and/or their complements as well as any of the peptides or proteins encoded thereby; (b) DNA vectors that contain a cDNA that substantially spans the entire open reading frame corresponding to any of the sequences of SEQ ID NOS:9-503 and/or their complements; (c) DNA expression vectors that have or contain any of the foregoing sequences, or a portion thereof, operatively associated with a (d) genetically engineered host cells that contain a cDNA that spans the entire open reading frame, or any portion thereof, corresponding to any of the sequences of SEQ ID NOS:9-503 operatively associated with a regulatory element, generally recombinantly positioned either *in vivo* (such as in gene activation) or *in vitro* that directs the expression of the coding sequences in the host cell. As used herein, regulatory elements include, but are not limited to,inducible and non-inducible promoters, enhancers, operators and other elements known to those skilled in the art that drive and regulate expression. Such regulatory elements include, but are not limited to,the baculovirus promoter, cytomegalovirus hCMV immediate early gene promoter, the early or late promoters of SV40 adenovirus, the *lac* system, the *trp* system, the *TAC* system, the *TRC* system, the major operator and promoter regions of phage A, the control regions of fd coat protein, acid phosphatase promoters, phosphoglycerate kinase (PGK) and especially 3-phosphoglycerate kinase promoters, and yeast alpha mating factors.

An additional application of the described novel human polynucleotide sequences is their use in the molecular mutagenesis/evolution of proteins that are at least partially encoded by the described novel sequences using, for example, polynucleotide shuffling or related methodologies. Such approaches are described in U.S. Patents Nos. 5,830,721 and 5,837,458 which are herein incorporated by reference in their entirety.

5.2 PROTEINS AND POLYPEPTIDES ENCODED BY POLYNUCLEOTIDES EXPRESSED IN MODIFIED HUMAN CELLS

Peptides and proteins encoded by the open reading frame of mRNAs corresponding to SEQ ID NOS:9-503, polypeptides and peptide fragments, mutated, truncated or deleted forms of those peptides and proteins, fusion proteins containing any of those peptides and proteins can be prepared for a variety of uses, including, but not limited to, the generation of antibodies, as reagents in diagnostic assays, the identification of other cellular gene products involved in the regulation of development and cellular differentiation of various cell types, like, for example, ES cells, as reagents in assays for screening for compounds that can be used in the treatment of disorders affecting development and cell differentiation, and as pharmaceutical reagents useful in the treatment of disorders affecting development and cell differentiation.

The invention also encompasses proteins, peptides, and polypeptides that are functionally equivalent to those encoded by SEQ ID NOS:9-503. Such functionally equivalent products include, but are not limited to, additions or substitutions of amino acid residues within the amino acid sequence encoded by the nucleotide sequences described above, but which result in a silent change, thus producing a functionally equivalent gene product. Amino acid substitutions can be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues involved. For example, nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, and methionine; polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine; positively charged (basic) amino acids include arginine, lysine, and histidine; and negatively charged (acidic) amino acids include aspartic acid and glutamic acid.

While random mutations can be introduced into DNA encoding peptides and proteins of the current invention (using random mutagenesis techniques well known to those skilled in the art), and the resulting mutant peptides and proteins tested for activity, site-directed mutations of the coding sequence can be engineered (using standard site-directed mutagenesis techniques) to generate mutant peptides and proteins of the current invention having increased functionality.

For example, the amino acid sequence of peptides and proteins of the current invention can be aligned with homologs from different species. Mutant peptides and proteins can be engineered so that regions of interspecies identity are maintained, whereas the variable residues are altered, *e.g.*, by deletion or insertion of an amino acid residue(s) or by substitution of one or more different amino acid residues. Conservative alterations at the variable positions can be engineered in order to produce a mutant form of a peptide or protein of the current invention that retains function. Non-conservative changes can be engineered at these variable positions to alter function. Alternatively, where alteration of function is desired, deletion or non-conservative alterations of the conserved regions can be engineered. One of skill in the art may easily test such mutant or deleted form of a peptide or protein of the current invention for these alterations in function using the teachings presented herein.

Other mutations to the coding sequences described above can be made to generate peptides and proteins that are better suited for expression, scale up, etc. in the host cells chosen. For example, the triplet code for each amino acid can be modified to conform more closely to the preferential codon usage of the host cell's translational machinery, or, for example, to yield a messenger RNA molecule with a longer half-life. Those skilled in the art would readily know what modifications of the nucleotide sequence would be desirable to conform the nucleotide sequence to preferential codon usage or to make the messenger RNA more stable. Such information would be obtainable, for example, through use of computer programs, through review of available research data on codon usage and messenger RNA stability, and through other means known to those of skill in the art.

Peptides corresponding to one or more domains (or a portion of a domain) of one of the proteins described above, truncated or deleted proteins, as well as fusion proteins in which the full length protein described above, a subunit peptide or truncated version is fused to an unrelated protein are also within the scope of the invention and can be designed by those of skill in the art on the basis of experimental or functional considerations. Such fusion proteins include, but are not limited to, fusions to an epitope tag; or fusions to an enzyme, fluorescent protein, or luminescent protein which provide a marker function.

While the peptides and proteins of the current invention can be chemically synthesized (*e.g.*, see Creighton, 1983, Proteins: Structures and Molecular Principles, W.H.

Freeman & Co., N.Y.), large polypeptides derived from any of the polynucleotides described above may advantageously be produced by recombinant DNA technology using techniques well known in the art for expressing genes and/or coding sequences. These methods include, for example, *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. See, for example, the techniques described in Sambrook *et al.*, 1989, *supra*, and Ausubel *et al.*, 1989, *supra*. Alternatively, RNA capable of encoding any of the nucleotide sequences described above may be chemically synthesized using, for example, synthesizers. See, for example, the techniques described in "Oligonucleotide Synthesis", 1984, Gait, M.J. ed., IRL Press, Oxford, which is incorporated by reference herein in its entirety.

A variety of host-expression vector systems may be utilized to express the nucleotide sequences of the invention. Where the peptide or protein to be synthesized is a soluble derivative, the peptide or polypeptide can be recovered from the culture, *i.e.*, from the host cell in cases where the peptide or polypeptide is not secreted, and from the culture media in cases where the peptide or polypeptide is secreted by the cells. However, such engineered host cells themselves may be used in situations where it is important not only to retain the structural and functional characteristics of the expressed peptide or protein, but to assess biological activity, *e.g.*, in drug screening assays.

The expression systems that may be used for purposes of the invention include, but are not limited to, microorganisms such as bacteria (*e.g.*, *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing a nucleotide sequence of the current invention; yeast (*e.g.*, *Saccharomyces*, *Pichia*) transformed with recombinant yeast expression vectors containing a nucleotide sequence of the current invention; insect cell systems infected with recombinant virus expression vectors (*e.g.*, baculovirus) containing a nucleotide sequence of the current invention; plant cell systems infected with recombinant virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (*e.g.*, Ti plasmid) containing a nucleotide sequence of the current invention; or mammalian cell systems (*e.g.*, COS, CHO, BHK, 293, 3T3, U937) harboring recombinant expression constructs containing promoters derived from the genome of

mammalian cells (*e.g.*, metallothionein promoter) or from mammalian viruses (*e.g.*, the adenovirus late promoter; the vaccinia virus 7.5K promoter).

In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the gene product being expressed. For example, when large quantities of such a protein are to be produced for the generation of pharmaceutical compositions of a protein or for raising antibodies to the protein to be expressed, for example, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited to, the *E. coli* expression vector pUR278 (Ruther *et al.*, 1983, EMBO J. *2*:1791), in which the coding sequence of the polynucleotide to be expressed may be ligated individually into the vector in frame with the *lacZ* coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, 1985, Nucleic Acids Res. *13*:3101-3109; Van Heeke & Schuster, 1989, J. Biol. Chem. *264*:5503-5509); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). If the inserted sequence encodes a relatively small polypeptide (less than 25 kD), such fusion proteins are generally soluble and can easily be purified from lysed cells by adsorption to glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety. Alternatively, if the resulting fusion protein is insoluble and forms inclusion bodies in the host cell, the inclusion bodies may be purified and the recombinant protein solubilized using techniques well known to one of skill in the art.

In an insect system, *Autographa californica* nuclear polyhidrosis virus (AcNPV) may be used as a vector to express foreign genes. (*e.g.*, see Smith *et al.*, 1983, J. Virol. *46*: 584; Smith, U.S. Patent No. 4,215,051). In one embodiment of the current invention, Sf9 insect cells are infected with a baculovirus vector expressing a peptide or protein of the current invention.

In mammalian host cells, a number of viral-based expression systems may be utilized. Specific embodiments (described more fully below) include the gene trap cDNA sequences of the current invention that are expressed by a CMV promoter to transiently express recombinant protein in U937 cells or in Cos-7 cells. Alternatively, retroviral vector systems

well known in the art may be used to insert the recombinant expression construct into host cells, or vaccinia virus-based expression systems may be employed.

In yeast, a number of vectors containing constitutive or inducible promoters may be used. For a review, see Current Protocols in Molecular Biology, Vol. 2, 1988, Ed. Ausubel *et al.*, Greene Publish. Assoc. & Wiley Interscience, Ch. 13; Grant *et al.*, 1987, Expression and Secretion Vectors for Yeast, in Methods in Enzymology, Eds. Wu & Grossman, 1987, Acad. Press, N.Y., Vol. 153, pp. 516-544; Glover, 1986, DNA Cloning, Vol. II, IRL Press, Wash., D.C., Ch. 3; and Bitter, 1987, Heterologous Gene Expression in Yeast, Methods in Enzymology, Eds. Berger & Kimmel, Acad. Press, N.Y., Vol. 152, pp. 673-684; and The Molecular Biology of the Yeast Saccharomyces, 1982, Eds. Strathern *et al.*, Cold Spring Harbor Press, Vols. I and II.

In cases where plant expression vectors are used, the expression of the coding sequence may be driven by any of a number of promoters. For example, viral promoters such as the 35S RNA and 19S RNA promoters of CaMV (Brisson *et al.*, 1984, Nature, *310*:511-514), or the coat protein promoter of TMV (Takamatsu *et al.*, 1987, EMBO J. *6*:307-311) may be used; alternatively, plant promoters such as the small subunit of RUBISCO (Coruzzi *et al.*, 1984, EMBO J. *3*:1671-1680; Broglie *et al.*, 1984, Science *224*:838-843); or heat shock promoters, *e.g.*, soybean hsp17.5-E or hsp17.3-B (Gurley *et al.*, 1986, Mol. Cell. Biol. 6:559-565) may be used. These constructs can be introduced into plant cells using Ti plasmids, Ri plasmids, plant virus vectors, direct DNA transformation, microinjection, electroporation, etc. For reviews of such techniques see, for example, Weissbach & Weissbach, 1988, Methods for Plant Molecular Biology, Academic Press, NY, Section VIII, pp. 421-463; and Grierson & Corey, 1988, Plant Molecular Biology, 2d Ed., Blackie, London, Ch. 7-9.

In cases where an adenovirus is used as an expression vector, the nucleotide sequence of interest may be ligated to an adenovirus transcription/translation control complex, *e.g.*, the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by *in vitro* or *in vivo* recombination. Insertion in a non-essential region of the viral genome (*e.g.*, region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the gene product of interest in infected hosts. (*e.g.*, See Logan & Shenk, 1984, Proc. Natl. Acad. Sci. USA *81*:3655-3659). Specific initiation signals may also

be required for efficient translation of inserted nucleotide sequences of interest. These signals include the ATG initiation codon and adjacent sequences. In cases where an entire gene or cDNA, including its own initiation codon and adjacent sequences, is inserted into the appropriate expression vector, no additional translational control signals may be needed. However, in cases where only a portion of a coding sequence of interest is inserted, exogenous translational control signals, including, perhaps, the ATG initiation codon, must be provided. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enchanter elements, transcription terminators, etc. (See Bittner *et al.*, 1987, Methods in Enzymol. *153*:516-544).

In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (*e.g.*, glycosylation) and processing (*e.g.*, cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript may be used. Such mammalian host cells include, but are not limited to,CHO, VERO, BHK, HeLa, COS, MDCK, 293, 3T3, WI38, and U937 cells.

For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the sequences of interest described above may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (*e.g.*, promoter, enchanter sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid

confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the gene product of interest. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that affect the endogenous activity of the gene product of interest.

A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler *et al.*, 1977, Cell *11*:223), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, 1962, Proc. Natl. Acad. Sci. USA *48*:2026), and adenine phosphoribosyltransferase (Lowy *et al.*, 1980, Cell *22*:817) genes can be employed in tk^-, $hgprt^-$ or $aprt^-$ cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler *et al.*, 1980, Natl. Acad. Sci. USA *77*:3567; O'Hare *et al.*, 1981, Proc. Natl. Acad. Sci. USA *78*:1527); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, 1981, Proc. Natl. Acad. Sci. USA *78*:2072); neo, which confers resistance to the aminoglycoside G-418 (Colberre-Garapin *et al.*, 1981, J. Mol. Biol. *150*:1); and hygro, which confers resistance to hygromycin (Santerre *et al.*, 1984, Gene *30*:147).

The gene products of interest can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, guinea pigs, pigs, micro-pigs, goats, and non-human primates, *e.g.*, baboons, monkeys, and chimpanzees may be used to generate transgenic animals carrying the polynucleotide of interest of the current invention.

Any technique known in the art may be used to introduce the transgene of interest into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to pronuclear microinjection (Hoppe, P.C. and Wagner, T.E., 1989, U.S. Pat. No. 4,873,191); retrovirus mediated gene transfer into germ lines (Van der Putten *et al.*, 1985, Proc. Natl. Acad. Sci., USA *82*:6148-6152); gene targeting in embryonic stem cells (Thompson *et al.*, 1989, Cell *56*:313-321); electroporation of embryos (Lo, 1983, Mol Cell. Biol. *3*:1803-1814); sperm-mediated gene transfer (Lavitrano *et al.*, 1989, Cell *57*:717-723); positive-negative selection as described in U.S. Patent No. 5,464,764 herein incorporated by reference. For a review of such techniques, see Gordon, 1989, Transgenic Animals, Intl. Rev. Cytol. *115*:171-229, which is incorporated by reference herein in its entirety.

The present invention provides for transgenic animals that carry the transgene of interest in all their cells, as well as animals which carry the transgene in some, but not all their cells, *i.e.*, mosaic animals. The transgene may be integrated as a single transgene or in concatamers, *e.g.*, head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko *et al.* (Lasko, M. *et al.*, 1992, Proc. Natl. Acad. Sci. USA *89*:6232-6236). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the transgene of interest be integrated into the chromosomal site of the endogenous copy of that same gene, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene of interest are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene of interest. In this way, the expression of the endogenous gene may also be eliminated by inserting non-functional sequences into the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene of interest in only that cell type, by following, for example, the teaching of Gu *et al.* (Gu *et al.*, 1994, Science *265*: 103-106). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest and will be apparent to those of skill in the art.

Once transgenic animals have been generated, the expression of the recombinant gene of interest may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to assay whether integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of cell type samples obtained from the animal, *in situ* hybridization analysis, and RT-PCR. Samples of gene-expressing tissue, may also be evaluated immunocytochemically using antibodies specific for the transgene product, as described below.

5.3 CELLS THAT CONTAIN A DISRUPTED ALLELE OF A GENE ENCODING A POLYNUCLEOTIDE OF THE CURRENT INVENTION

Another aspect of the current invention are cells which contain a gene that encodes a polynucleotide of the current invention and that has been disrupted. Those of skill in the art would know how to disrupt a gene in a cell using techniques known in the art. Also, techniques useful to disrupt a gene in a cell and especially an ES cell, that may already be disrupted, as disclosed in copending US patent applications Nos. 08/726,867; 08/728,963; 08/907,598; and 08/942,806, all of which are hereby incorporated herein by reference in their entirety, are within the scope of the current invention to disrupt a gene that encodes a polynucleotide of the current invention.

5.3.1 IDENTIFICATION OF CELLS THAT EXPRESS GENES ENCODING POLYNUCLEOTIDES OF THE CURRENT INVENTION

Host cells that contain coding sequence and/or express a biologically active gene product, or fragment thereof, encoded by a gene corresponding to a GTS present invention may be identified by at least four general approaches; (a) DNA-DNA or DNA-RNA hybridization; (b) the presence or absence of "marker" gene functions; (c) assessing the level of transcription as measured by the expression of mRNA transcripts in the host cell; and (d) detection of the gene product as measured by immunoassay, enzymatic assay, chemical assay, or by its biological activity. Prior to screening for gene expression, the host cells can first be treated in an effort to increase the level of expression of genes encoding polynucleotides of the current invention, especially in cell lines that produce low amounts of the mRNAs and/or peptides and proteins of the current invention.

In the first approach, the presence of the coding sequence for peptides and proteins of the current invention inserted in the expression vector can be detected by DNA-DNA or DNA-RNA hybridization using probes comprising nucleotide sequences that are homologous to the coding sequence for peptides and proteins of the current invention, respectively, or portions or derivatives thereof.

In the second approach, the recombinant expression vector/host system can be identified and selected based upon the presence or absence of certain "marker" gene functions

(*e.g.*, thymidine kinase activity, resistance to antibiotics, resistance to methotrexate, transformation phenotype, occlusion body formation in baculovirus, etc.). For example, if the coding sequence for the peptide or protein of the current invention is inserted within a marker gene sequence of the vector, recombinants containing the coding sequence for the peptide or protein of the current invention can be identified by the absence of the marker gene function. Alternatively, a marker gene can be placed in tandem with the sequence for the peptide or protein of the current invention under the control of the same or different promoter used to control the expression of the coding sequence for the peptide or protein of the current invention. Expression of the marker in response to induction or selection indicates expression of the coding sequence for the peptide or protein of the current invention.

In the third approach, transcriptional activity for the coding region of genes specific for peptides and proteins of the current invention can be assessed by hybridization assays. For example, RNA can be isolated and analyzed by Northern blot using a probe derived from a GTS, or any portion thereof. Alternatively, total nucleic acids of the host cell may be extracted and assayed for hybridization to such probes. Additionally, RT-PCR (using GTS specific oligos/products) may be used to detect low levels of gene expression in a sample, or in RNA isolated from a spectrum of different tissues, or PCR can be used can be used to screen a variety of cDNA libraries derived from different tissues to determine which tissues express a given GTS.

In the fourth approach, the expression of the peptides and proteins of the current invention can be assessed immunologically, for example by Western blots, immunoassays such as radioimmuno-precipitation, enzyme-linked immunoassays and the like. This can be achieved by using an antibody and a binding partner specific to a peptide or protein of the current invention.

5.4 ANTIBODIES TO PROTEINS OF THE CURRENT INVENTION

Antibodies that specifically recognize one or more epitopes of a peptide or protein of the current invention, or epitopes of conserved variants of a peptide or protein at least partially encoded by a GTS of the present invention, or any and all peptide fragments thereof, are also encompassed by the invention. Such antibodies include, but are not limited

to,polyclonal antibodies, monoclonal antibodies (mAbs), humanized or chimeric antibodies, single chain antibodies, Fab fragments, $F(ab')_2$ fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above.

The antibodies of the invention may be used, for example, in the detection of the peptide or protein of interest of the current invention in a biological sample and may, therefore, be utilized as part of a diagnostic or prognostic technique whereby patients may be tested for abnormal amounts of these proteins. Such antibodies may also be utilized in conjunction with, for example, compound screening schemes as described, below in Section 5.6 for the evaluation of the effect of test compounds on expression and/or activity of the gene products of interest of the current invention. Additionally, such antibodies can be used in conjunction with the gene therapy and gene delivery techniques described below to, for example, evaluate the normal and/or engineered peptide- or protein-expressing cells prior to their introduction into the patient. Such antibodies may additionally be used as a method for inhibiting the abnormal activity of a peptide or protein of interest at least partially encoded by a GTS of the present invention. Thus, such antibodies may, for example, be utilized as part of treatment methods for development and cell differentiation disorders.

For the production of antibodies, various host animals may be immunized by injection with the peptide or protein of interest, a subunit peptide of such protein, a truncated polypeptide, functional equivalents of the peptide or protein, mutants of the peptide or protein, or denatured forms of the above. Such host animals may include, but are not limited to,rabbits, mice, and rats, to name but a few. Various adjuvants can be used to increase the immunological response, depending on the host species, including but not limited to Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanin, dinitrophenol, and potentially useful human adjutants such as BCG (bacille Calmette-Guerin) and *Corynebacterium parvum*. Polyclonal antibodies are heterogeneous populations of antibody molecules derived from the sera of the immunized animals.

Monoclonal antibodies, which are homogeneous populations of antibodies to a particular antigen, may be obtained by any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique of Kohler and Milstein, (1975, Nature *256*:495-497; and U.S. Patent No. 4,376,110), the human B-cell hybridoma technique (Kosbor *et al.*, 1983, Immunology Today *4*:72; Cole *et al.*, 1983, Proc. Natl. Acad. Sci. USA *80*:2026-2030), and the EBV-hybridoma technique (Cole *et al.*, 1985, Monoclonal Antibodies And Cancer Therapy, Alan R. Liss, Inc., pp. 77-96). Such antibodies may be of any immunoglobulin class including IgG, IgM, IgE, IgA, IgD and any subclass thereof. The hybridoma producing the mAb of this invention may be cultivated *in vitro* or *in vivo*. Production of high titers of mAbs *in vivo* makes this the presently preferred method of production.

In addition, techniques developed for the production of "chimeric antibodies" (Morrison *et al.*, 1984, Proc. Natl. Acad. Sci. USA, *81*:6851-6855; Neuberger *et al.*, 1984, Nature, *312*:604-608; Takeda *et al.*, 1985, Nature, *314*:452-454) by splicing the genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a porcine mAb and a human immunoglobulin constant region.

Alternatively, techniques described for the production of single chain antibodies (U.S. Patent 4,946,778; Bird, 1988, Science *242*:423-426; Huston *et al.*, 1988, Proc. Natl. Acad. Sci. USA *85*:5879-5883; and Ward *et al.*, 1989, Nature *334*:544-546) can be adapted to produce single chain antibodies against gene products of interest. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide.

Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, such fragments include, but are not limited to: the $F(ab')_2$ fragments which can be produced by pepsin digestion of the antibody molecule and the Fab fragments which can be generated by reducing the disulfide bridges of the $F(ab')_2$ fragments. Alternatively, Fab expression libraries may be constructed (Huse *et al.*, 1989, Science,

246:1275-1281) to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity.

Antibodies to peptides and proteins that are fully or at least partially encoded by the described GTSs, or fragments or truncated versions thereof, can in turn be utilized to generate anti-idiotypic antibodies that "mimic" an epitope of the peptide or protein of interest, using techniques well known to those skilled in the art. (See, *e.g.*, Greenspan & Bona, 1993, FASEB J *7(5)*:437-444; and Nissinoff, 1991, J. Immunol. *147(8)*:2429-2438). For example antibodies that bind to a regulatory peptide or protein of interest of the current invention and competitively inhibit the binding of such peptide or protein to any of its binding partners in the cell can be used to generate anti-idiotypes that "mimic" the peptide or protein of interest and, therefore, bind and neutralize the particular binding partner of the peptide or protein of interest. Such neutralizing antibodies, anti-idiotypes, Fab fragments of such antibodies, or humanized derivatives thereof, can be used in therapeutic regimens to mimic or neutralize (depending on the antibody) the effect of a particular peptide of interest, or a binding partner of a peptide or protein of interest.

5.5 DIAGNOSIS OF DISORDERS AFFECTING DEVELOPMENT AND CELL DIFFERENTIATION

A variety of methods can be employed for the diagnostic and prognostic evaluation of disorders involving developmental and differentiation processes, and for the identification of subjects having a predisposition to such disorders.

Such methods may, for example, utilize reagents such as the nucleotide sequences described above, and antibodies to peptides and proteins of the current invention, as described, in Section 5.4. Specifically, such reagents may be used, for example, for: (1) the detection of the presence of gene mutations, or the detection of either over- or under-expression of the respective mRNAs relative to the non-disorder state; (2) the detection of either an over- or an under-abundance of the respective gene product relative to the non-disorder state; and (3) the detection of perturbations or abnormalities in the intra- and inter-cellular processes mediated by the respective peptides or proteins of the current invention.

The methods described herein may be performed, for example, by utilizing pre-packaged diagnostic kits comprising at least one specific nucleotide sequence of the current invention or antibody reagent described herein, which may be conveniently used, *e.g.*, in clinical settings, to diagnose patients exhibiting developmental or cell differentiation disorder abnormalities.

For the detection of mutations in any of the genes described above, any nucleated cell can be used as a starting source for genomic nucleic acid. For the detection of gene expression or gene products, any cell type or tissue in which the gene of interest is expressed, such as, for example, ES cells, may be utilized. Specific examples of cells and tissues that can be analyzed using the claimed polynucleotides include, but are not limited to, endothelial cells, epithelial cells, islets, neurons or neural tissue, mesothelial cells, osteocytes, lymphocytes, chondrocytes, hematopoietic cells, immune cells, cells of the major glands or organs (e.g., lung, heart, stomach, pancreas, kidney, skin, etc.), exocrine and/or endocrine cells, embryonic and other stem cells, fibroblasts, and culture adapted and/or transformed versions of the above. Diseases or natural processes that can also be correlated with the expression of mutant, or normal, variants of the disclosed GTSs include, but are not limited to, aging, cancer, autoimmune disease, lupus, scleroderma, Crohn's disease, multiple sclerosis, inflammatory bowel disease, immune disorders, schizophrenia, psychosis, alopecia, glandular disorders, inflammatory disorders, ataxia telangiectasia, diabetes, skin disorders such as acne, eczema, and the like, osteo and rheumatoid arthritis, high blood pressure, atherosclerosis, cardiovascular disease, pulmonary disease, degenerative diseases of the neural or skeletal systems, Alzheimer's disease, Parkinson's disease, osteoporosis, asthma, developmental disorders or abnormalities, genetic birth defects, infertility, epithelial ulcerations, and viral, parasitic, fungal, yeast, or bacterial infection.

Primary, secondary, or culture-adapted variants of cancer cells/tissues can also be analyzed using the claimed polynucleotides. Examples of such cancers include, but are not limited to, Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous

hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor, chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiforme, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord (neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, endometrioid tumors, celioblastoma, clear cell carcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma [embryonal rhabdomyosarcoma], fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's

disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles, dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; Breast: carcinoma and sarcoma, and Adrenal glands: neuroblastoma.

Nucleic acid-based detection techniques and peptide detection techniques that can be used to conduct the above analyses are described below.

5.5.1. DETECTION OF THE GENES OF THE CURRENT INVENTION AND THEIR RESPECTIVE TRANSCRIPTS

Mutations within the genes of the current invention can be detected by utilizing a number of techniques. Nucleic acid from any nucleated cell can be used as the starting point for such assay techniques, and may be isolated according to standard nucleic acid preparation procedures which are well known to those of skill in the art.

DNA may be used in hybridization or amplification assays of biological samples to detect abnormalities involving gene structure, including point mutations, insertions, deletions and chromosomal rearrangements. Such assays may include, but are not limited to, Southern analyses, single stranded conformational polymorphism analyses (SSCP), and PCR analyses.

Such diagnostic methods for the detection of gene-specific mutations can involve for example, contacting and incubating nucleic acids including recombinant DNA molecules, cloned genes or degenerate variants thereof, obtained from a sample, *e.g.*, derived from a patient sample or other appropriate cellular source, with one or more labeled nucleic acid reagents including recombinant DNA molecules, cloned genes or degenerate variants thereof, as described above, under conditions favorable for the specific annealing of these reagents to their complementary sequences within the gene of interest of the current invention. Preferably, the lengths of these nucleic acid reagents are at least 15 to 30 nucleotides. After incubation, all non-annealed nucleic acids are removed from the nucleic acid molecule hybrid. The presence of nucleic acids which have hybridized, if any such molecules exist, is then detected. Using such a detection scheme, the nucleic acid from the cell type or tissue of interest can be immobilized, for example, to a solid support such as a membrane, or a plastic surface such as that on a microtiter plate or polystyrene beads. In this case, after incubation,

non-annealed, labeled nucleic acid reagents of the type described above are easily removed. Detection of the remaining, annealed, labeled nucleic acid reagents is accomplished using standard techniques well-known to those in the art. The gene sequences to which the nucleic acid reagents have annealed can be compared to the annealing pattern expected from a normal gene sequence in order to determine whether a gene mutation is present.

Alternative diagnostic methods for the detection of gene specific nucleic acid molecules, in patient samples or other appropriate cell sources, may involve their amplification, *e.g.*, by PCR (the experimental embodiment set forth in Mullis, K.B., 1987, U.S. Patent No. 4,683,202), followed by the detection of the amplified molecules using techniques well known to those of skill in the art. The resulting amplified sequences can be compared to those which would be expected if the nucleic acid being amplified contained only normal copies of the respective gene in order to determine whether a gene mutation exists.

Additionally, well-known genotyping techniques can be performed to identify individuals carrying mutations in any of the genes of the current invention. Such techniques include, for example, the use of restriction fragment length polymorphisms (RFLPs), which involve sequence variations in one of the recognition sites for the specific restriction enzyme used.

Furthermore, the polynucleotide sequences of the current invention may be mapped to chromosomes and specific regions of chromosomes using well known genetic and/or chromosomal mapping techniques. These techniques include *in situ* hybridization, linkage analysis against known chromosomal markers, hybridization screening with libraries or flow-sorted chromosomal preparations specific to known chromosomes, and the like. The technique of fluorescent *in situ* hybridization of chromosome spreads has been described, for example, in Verma *et al.* (1988) Human Chromosomes: A Manual of Basic Techniques, Pergamon Press, New York. Fluorescent *in situ* hybridization of chromosomal preparations and other physical chromosome mapping techniques may be correlated with additional genetic map data. Examples of genetic map data can be found, for example, in Genetic Maps: Locus Maps of Complex Genomes, Book 5: Human Maps, O'Brien, editor, Cold

Spring Harbor Laboratory Press (1990). Comparisons of physical chromosomal map data may be of particular interest in detecting genetic diseases in carrier states.

The level of expression of genes can also be assayed by detecting and measuring the transcription of such genes. For example, RNA from a cell type or tissue known, or suspected to express any of the genes of the current invention can be isolated and tested utilizing hybridization or PCR techniques (e.g., northern or RT PCR) such as those described, above. Such analyses may reveal both quantitative and qualitative aspects of the expression pattern of the respective gene, including activation or inactivation of gene expression. *In situ* hybridization using suitable radioactive labels, enzymatic labels, or chemically tagged forms of the described polynucleotide sequences can also be used to assess expression patterns *in vivo*.

Additionally, an oligonucleotide or polynucleotide sequence first disclosed in at least a portion of one of the GTS sequences of SEQ ID NOS:9-503 can be used as a hybridization probe in conjunction with a solid support matrix/substrate (resins, beads, membranes, plastics, polymers, metal or metallized substrates, crystalline or polycrystalline substrates, etc.). Of particular note are spatially addressable arrays (*i.e.*, gene chips, microtiter plates, etc.) of oligonucleotides and polynucleotides, or corresponding oligopeptides and polypeptides, wherein at least one of the biopolymers present on the spatially addressable array comprises an oligonucleotide or polynucleotide sequence first disclosed in at least one of the GTS sequences of SEQ ID NOS:9-503, or an amino acid sequence encoded thereby. Methods for attaching biopolymers to, or synthesizing biopolymers on, solid support matrices, and conducting binding studies thereon are disclosed in, *inter alia*, U.S. Patent Nos. 5,556,752, 5,744,305, 4,631,211, 5,445,934, 5,252,743, 4,713,326, 5,424,186, and 4,689,405 the disclosures of which are herein incorporated by reference in their entirety.

Oligonucleotides corresponding to the described GTSs can be used as hybridization probes either singly or in chip format. For example, a series of such GTS oligonucleotide sequences, or the complements thereof, can be used to represent all or a portion of the described GTS sequences. The oligonucleotides, typically between about 16 to about 40 (or any whole number within the stated range) nucleotides in length, may partially overlap each other and/or the NHP sequence may be represented using oligonucleotides that do not

overlap. Accordingly, the described NHP polynucleotide sequences shall typically comprise at least about two or three distinct oligonucleotide sequences of at least about 18, and preferably about 25, nucleotides in length that are first disclosed in the described Sequence Listing. Such oligonucleotide sequences may begin at any nucleotide present within a sequence in the Sequence Listing and proceed in either a sense (5'-to-3') orientation vis-a-vis the described sequence or in an antisense orientation.

Although the presently described GTSs have been specifically described using nucleotide sequence, it should be appreciated that each of the GTSs can uniquely be described using any of a wide variety of additional structural attributes, or combinations thereof. For example, a given GTS can be described by the net composition of the nucleotides present within a given region of the GTS in conjunction with the presence of one or more specific oligonucleotide sequence(s) first disclosed in the GTS. Alternatively, a restriction map specifying the relative positions of restriction endonuclease digestion sites, or various palindromic or other specific oligonucleotide sequences can be used to structurally describe a given GTS. Such restriction maps, which are typically generated by widely available computer programs (*e.g.*, the University of Wisconsin GCG sequence analysis package, SEQUENCHER 3.0, Gene Codes Corp., Ann Arbor, MI, etc.), can optionally be used in conjunction with one or more discrete nucleotide sequence(s) present in the GTS that can be described by the relative position of the sequence relative to one or more additional sequence(s) or one or more restriction sites present in the GTS.

5.5.2 DETECTION OF THE GENE PRODUCTS OF THE CURRENT INVENTION

Antibodies directed against wild type or mutant gene products of the current invention or conserved variants or peptide fragments thereof, which are discussed above in Section 5.4 may also be used as diagnostics and prognostics for disorders affecting development and cellular differentiation, as described herein. Such diagnostic methods, may be used to detect abnormalities in the level of gene expression, or abnormalities in the structure and/or temporal, tissue, cellular, or subcellular location of the respective gene product, and may be performed *in vivo* or *in vitro*, such as, for example, on biopsy tissue.

The tissue or cell type to be analyzed will generally include those which are known, or suspected, to contain cells that express the respective gene. The protein isolation methods employed herein may, for example, be such as those described in Harlow and Lane (Harlow, E. and Lane, D., 1988, "Antibodies: A Laboratory Manual", Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York), which is incorporated herein by reference in its entirety. The isolated cells can be derived from cell culture or from a patient. The analysis of cells taken from culture may be a necessary step in the assessment of cells that could be used as part of a cell-based gene therapy technique or, alternatively, to test the effect of compounds on the expression of the respective gene.

For example, antibodies, or fragments of antibodies, such as those described above in Section 5.4 are also useful in the present invention to quantitatively or qualitatively detect the presence of gene products of the current invention or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody (see below, this Section) coupled with light microscopic, flow cytometric, or fluorimetric detection.

The antibodies (or fragments thereof) or fusion or conjugated proteins useful in the present invention may, additionally, be employed histologically, as in immunofluorescence, immunoelectron microscopy or non-immuno assays, for *in situ* detection of gene products of the current invention or conserved variants or peptide fragments thereof, or for catalytic subunit binding (in the case of labeled catalytic subunit fusion protein).

In situ detection may be accomplished by removing a histological specimen from a patient, and applying thereto a labeled antibody or fusion protein of the present invention. The antibody (or fragment) or fusion protein is preferably applied by overlaying the labeled antibody (or fragment) onto a biological sample. Through the use of such a procedure, it is possible to determine not only the presence of the gene product of the current invention, or conserved variants or peptide fragments, but also its distribution in the examined tissue. Using the present invention, those of ordinary skill will readily perceive that any of a wide variety of histological methods (such as staining procedures) can be modified in order to achieve such *in situ* detection.

Immunoassays and non-immunoassays for gene products of the current invention or conserved variants or peptide fragments thereof will typically comprise incubating a sample, such as a biological fluid, a tissue extract, freshly harvested cells, or lysates of cells which have been incubated in cell culture, in the presence of a detectably labeled antibody capable of identifying the respective gene products of interest or conserved variants or peptide fragments thereof, and detecting the bound antibody by any of a number of techniques well-known in the art.

The biological sample may be brought in contact with and immobilized onto a solid phase support or carrier such as nitrocellulose, or other solid support which is capable of immobilizing cells, cell particles or soluble proteins. The support may then be washed with suitable buffers followed by treatment with the detectably labeled antibody specific to the peptide or protein of interest of the current invention or with fusion protein. The solid phase support may then be washed with the buffer a second time to remove unbound antibody or fusion protein. The amount of bound label on solid support may then be detected by conventional means.

"Solid phase support or carrier" is intended to encompass any support capable of binding an antigen or an antibody. Well-known supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite. The nature of the carrier can be either soluble to some extent or insoluble for the purposes of the present invention. The support material may have virtually any possible structural configuration so long as the coupled molecule is capable of binding to an antigen or antibody. Thus, the support configuration may be spherical, as in a bead, or cylindrical, as in the inside surface of a test tube, or the external surface of a rod. Alternatively, the surface may be flat such as a sheet, test strip, etc. Preferred supports include polystyrene beads. Those skilled in the art will know many other suitable carriers for binding antibody or antigen, or will be able to ascertain the same by use of routine experimentation.

The binding activity of a given lot of antibody or fusion protein may be determined according to well known methods. Those skilled in the art will be able to determine operative and optimal assay conditions for each determination by employing routine experimentation.

With respect to antibodies, one of the ways in which the antibody can be detectably labeled is by linking the same to an enzyme and use in an enzyme immunoassay (EIA) (Voller, "The Enzyme Linked Immunosorbent Assay (ELISA)", 1978, Diagnostic Horizons *2*:1-7, Microbiological Associates Quarterly Publication, Walkersville, MD); Voller *et al.*, 1978, J. Clin. Pathol. *31*:507-520; Butler, 1981, Meth. Enzymol. *73*:482-523; Maggio (ed.), 1980, Enzyme Immunoassay, CRC Press, Boca Raton, FL,; Ishikawa *et al.*, (eds.), 1981, Enzyme Immunoassay, Kgaku Shoin, Tokyo). The enzyme which is bound to the antibody will react with an appropriate substrate, preferably a chromogenic substrate, in such a manner as to produce a chemical moiety which can be detected, for example, by spectrophotometric, fluorimetric or by visual means. Enzymes which can be used to detectably label the antibody include, but are not limited to, malate dehydrogenase, staphylococcal nuclease, delta-5-steroid isomerase, yeast alcohol dehydrogenase, alpha-glycerophosphate, dehydrogenase, triose phosphate isomerase, horseradish peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, beta-galactosidase, ribonuclease, urease, catalase, glucose-6-phosphate dehydrogenase, glucoamylase and acetylcholinesterase. The detection can be accomplished by colorimetric methods which employ a chromogenic substrate for the enzyme. Detection may also be accomplished by visual comparison of the extent of enzymatic reaction of a substrate in comparison with similarly prepared standards.

Detection may also be accomplished using any of a variety of other immunoassays. For example, by radioactively labeling the antibodies or antibody fragments, it is possible to detect the peptide or protein of interest through the use of a radioimmunoassay (RIA) (see, for example, Weintraub, B., Principles of Radioimmunoassays, Seventh Training Course on Radioligand Assay Techniques, The Endocrine Society, March, 1986, which is incorporated by reference herein). The radioactive isotope can be detected by such means as the use of a gamma counter or a scintillation counter or by autoradiography.

It is also possible to label the antibody with a fluorescent compound. When the fluorescently labeled antibody is exposed to light of the proper wave length, its presence can then be detected due to fluorescence. Among the most commonly used fluorescent labeling compounds are fluorescein isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin and fluorescamine.

The antibody can also be detectably labeled using fluorescence emitting metals such as ^{152}Eu, or others of the lanthanide series. These metals can be attached to the antibody using such metal chelating groups as diethylenetriaminepentacetic acid (DTPA) or ethylenediaminetetraacetic acid (EDTA).

The antibody also can be detectably labeled by coupling it to a chemiluminescent compound. The presence of the chemiluminescent-tagged antibody is then determined by detecting the presence of luminescence that arises during the course of a chemical reaction. Examples of particularly useful chemiluminescent labeling compounds are luminol, isoluminol, theromatic acridinium ester, imidazole, acridinium salt and oxalate ester.

Likewise, a bioluminescent compound may be used to label the antibody of the present invention. Bioluminescence is a type of chemiluminescence found in biological systems in, which a catalytic protein increases the efficiency of the chemiluminescent reaction. The presence of a bioluminescent protein is determined by detecting the presence of luminescence. Important bioluminescent compounds for labeling purposes include, but are not limited to, luciferin, luciferase and aequorin.

An additional use of a peptide or polypeptide encoded by an oligonucleotide or polynucleotide sequence first disclosed in at least one of the GTS sequences of SEQ ID NOS:9-503 is by incorporating the sequence into a phage display, or other peptide library/binding, system that can be used to screen for proteins, or other ligands, that are capable of binding to an amino acid sequence encoded by an oligonucleotide or polynucleotide sequence first disclosed in at least one of the GTS sequences of SEQ ID NOS:9-503 (see U.S. Patents Nos. 5,270,170, and 5,432,018, herein incorporated by reference in their entirety). Moreover, peptide arrays comprising a novel amino acid sequence corresponding to a portion of at least one of the polynucleotide sequences first disclosed in SEQ ID NOS:9-503 can be generated and screened essentially as described in U.S. Patents Nos. 5,143,854, 5,405,783, and 5,252,743, the complete disclosures of which are herein incorporated by references.

Additionally, the presently described GTSs, or primers derived therefrom, can be used to screen spatially addressable arrays, or pools therefrom, of clones present in a full-length human cDNA library. The 96 well microtiter plate format is especially well-suited to the

screening, by PCR for example, of pooled subfractions of cDNA clones.

5.6 SCREENING ASSAYS FOR COMPOUNDS THAT MODULATE THE EXPRESSION OR ACTIVITY OF PEPTIDES AND PROTEINS OF THE CURRENT INVENTION

The following assays are designed to identify compounds that interact with (*e.g.*, bind to) peptides and proteins at least partially encoded by one of SEQ ID NOS:9-503 (i.e. peptides or proteins of the current invention) compounds that interact with (*e.g.*, bind to) intracellular proteins that interact with peptides and proteins of the current invention, compounds that interfere with the interaction of peptides and proteins of the current invention with each other and with other intracellular proteins involved in developmental and cell differentiation processes, and to compounds which modulate the activity of genes of the current invention (*i.e.*, modulate the level of expression of genes of the current invention) or modulate the level of gene products of the current invention. Assays may additionally be utilized which identify compounds which bind to gene regulatory sequences (*e.g.*, promoter sequences) and which may modulate the expression of genes of the current invention. See *e.g.*, Platt, K.A., 1994, J. Biol. Chem. 269:28558-28562, which is incorporated herein by reference in its entirety.

Compounds that can be screened in accordance with the invention include, but are not limited to, peptides, antibodies and fragments thereof, prostaglandins, lipids and other organic compounds (*e.g.*, terpines, peptidomimetics) that bind to the peptide or protein of interest of the current invention and either mimic the activity triggered by the natural ligand (*i.e.*, agonists) or inhibit the activity triggered by the natural ligand (*i.e.*, antagonists); as well as peptides, antibodies or fragments thereof, and other organic compounds that mimic the peptide or protein of interest of the current invention (or a portion thereof) and bind to and "neutralize" natural ligand.

Such compounds may include, but are not limited to, peptides such as, for example, soluble peptides, including but not limited to members of random peptide libraries (see, *e.g.*, Lam, K.S. *et al.*, 1991, Nature 354:82-84; Houghten, R. *et al.*, 1991, Nature 354:84-86), and combinatorial chemistry-derived molecular library peptides made of D- and/or L-configuration amino acids, phosphopeptides (including, but not limited to, members of

random or partially degenerate, directed phosphopeptide libraries; see, *e.g.*, Songyang, Z. *et al.*, 1993, Cell 72:767-778); antibodies (including, but not limited to, polyclonal, monoclonal, humanized, anti-idiotypic, chimeric or single chain antibodies, and Fab, $F(ab')_2$ and Fab expression library fragments, and epitope-binding fragments thereof); and small organic or inorganic molecules.

Other compounds that can be screened in accordance with the invention include, but are not limited to, small organic molecules that are able to gain entry into an appropriate cell (*e.g.*, in ES cells) and affect the expression of a gene of the current invention or some other gene involved in development and cell differentiation (*e.g.*, by interacting with the regulatory region or transcription factors involved in gene expression); or such compounds that affect the activity of the peptide or protein of interest of the current invention, *e.g.*, by inhibiting or enhancing the binding of such peptide or protein to another cellular peptide or protein, or other factor, necessary for catalysis, signal transduction, or the like, that is involved in developmental or cell differentiation processes.

Computer modeling and searching technologies permit the identification of compounds, or the improvement of already identified compounds, that can modulate the expression or activity of peptides or proteins of interest of the current invention. Having identified such a compound or composition, the active sites or regions are identified. Such active sites might typically be the binding partner sites, such as, for example, the interaction domains of the peptides and proteins of the current invention with their respective binding partners. The active site can be identified using methods known in the art including, for example, from study of the amino acid sequences of peptides, from the nucleotide sequences of nucleic acids, or from study of complexes of the relevant compound or composition with its natural ligand. In the latter case, chemical or X-ray crystallographic methods can be used to find the active site by finding where on the factor the complexed ligand is found.

Next, the three dimensional geometric structure of the active site is determined. This can be done by known methods, including X-ray crystallography, which can determine a complete molecular structure. On the other hand, solid or liquid phase NMR can be used to determine certain intra-molecular distances. Any other experimental method of structure determination can be used to obtain partial or complete geometric structures. The geometric

structures may be measured with a complexed ligand, natural or artificial, which may increase the accuracy of the active site structure determined.

If an incomplete or insufficiently accurate structure is determined, the methods of computer based numerical modeling can be used to complete the structure or improve its accuracy. Any recognized modeling method may be used, including parameterized models specific to particular biopolymers such as proteins or nucleic acids, molecular dynamics models based on computing molecular motions, statistical mechanics models based on thermal ensembles, or combined models. For most types of models, standard molecular force fields, representing the forces between constituent atoms and groups, are necessary, and can be selected from force fields known in physical chemistry. The incomplete or less accurate experimental structures can serve as constraints on the complete and more accurate structures computed by these modeling methods.

Finally, having determined the structure of the active site, either experimentally, by modeling, or by a combination, candidate modulating compounds can be identified by searching databases containing compounds along with information on their molecular structure. Such a search seeks compounds having structures that match the determined active site structure and that interact with the groups defining the active site. Such a search can be manual, but is preferably computer assisted. These compounds found from this search are potential modulating compounds of the peptides and proteins of interest of the current invention.

Alternatively, these methods can be used to identify improved modulating compounds from an already known modulating compound or ligand. The composition of the known compound can be modified and the structural effects of modification can be determined using the experimental and computer modeling methods described above applied to the new composition. The altered structure is then compared to the active site structure of the compound to determine if an improved fit or interaction results. In this manner, systematic variations in composition, such as by varying side groups, can be quickly evaluated to obtain modified modulating compounds or ligands of improved specificity or activity.

Further experimental and computer modeling methods useful to identify modulating compounds based upon identification of the active sites of peptides and proteins of interest of

the current invention, and related factors involved in development, cellular differentiation, and other cellular processes will be apparent to those of skill in the art.

Examples of molecular modeling systems are the CHARM and QUANTA programs (Polygon Corporation, Waltham, MA). CHARM performs the energy minimization and molecular dynamics functions. QUANTA performs the construction, graphic modeling and analysis of molecular structure. QUANTA allows interactive construction, modification, visualization, and analysis of the behavior of molecules with each other.

A number of articles review computer modeling of drugs interactive with specific proteins, such as Rotivinen *et al.*, 1988, Acta Pharmaceutical Fennica *97*:159-166; Ripka, New Scientist 54-57 (June 16, 1988); McKinaly and Rossmann, 1989, Annu. Rev. Pharmacol. Toxicol. *29*:111-122; Perry and Davies, OSAR: Quantitative Structure-Activity Relationships in Drug Design pp. 189-193 (Alan R. Liss, Inc. 1989); Lewis and Dean, 1989, Proc. R. Soc. Lond. *236*:125-140 and 141-162; and, with respect to a model receptor for nucleic acid components, Askew *et al.*, 1989, J. Am. Chem. Soc. *111*:1082-1090. Other computer programs that screen and graphically depict chemicals are available from companies such as BioDesign, Inc. (Pasadena, CA.), Allelix, Inc. (Mississauga, Ontario, Canada), and Hypercube, Inc. (Cambridge, Ontario). Although these are primarily designed for application to drugs specific to particular proteins, they can be adapted to the design of drugs specific to regions of DNA or RNA, once that region is identified.

Although described above with reference to design and generation of compounds which could alter binding, one could also screen libraries of known compounds, including natural products or synthetic chemicals, and biologically active materials, including proteins, for compounds which are inhibitors or activators.

Compounds identified via assays such as those described herein may be useful, for example, in elaborating the biological function of the gene products of interest of the current invention and for ameliorating disorders affecting development and cell differentiation. Assays for testing the effectiveness of compounds, identified by, for example, techniques such as those described below.

5.6.1. *IN VITRO* SCREENING ASSAYS FOR COMPOUNDS THAT BIND TO PEPTIDES AND PROTEINS OF THE CURRENT INVENTION

In vitro systems may be designed to identify compounds capable of interacting with (*e.g.*, binding to) peptides and proteins of interest of the current invention, fragments thereof, and variants thereof. The identified compounds can be useful, for example, in modulating the activity of wild type and/or mutant gene products of the current invention; may be utilized in screens for identifying compounds that disrupt normal interactions of the peptides and proteins of the current invention with other factors, like, for example, other peptides and proteins; or may in themselves disrupt such interactions.

The principle of the assays used to identify compounds that bind to the peptides and proteins of the current invention involves preparing a reaction mixture of the peptides and proteins of interest that are disclosed by the current invention and a test compound under conditions and for a time sufficient to allow the two components to interact and bind, thus forming a complex that can be removed from and/or detected in the reaction mixture. The peptides and proteins of the current invention used can vary depending upon the goal of the screening assay. For example, where agonists of the natural ligand are sought, the full length peptide or protein of interest, or a fusion protein containing the subunit of interest fused to a protein or polypeptide that affords advantages in the assay system (*e.g.*, labeling, isolation of the resulting complex, etc.) can be utilized.

The screening assays can be conducted in a variety of ways. For example, one method of conducting such an assay involves anchoring the peptide or protein of interest, or a fragment or fusion protein thereof, or the test substance onto a solid phase and detecting peptide or protein of interest/test compound complexes anchored on the solid phase at the end of the reaction. In one embodiment of such a method, the peptide or protein of interest may be anchored onto a solid surface, and the test compound, which is not anchored, may be labeled, either directly or indirectly. In another embodiment of the method, a peptide or protein of interest of the current invention anchored on the solid phase is complexed with a natural ligand of such peptide or protein of interest. Then, a test compound could be assayed for its ability to disrupt the association of the complex.

In practice, microtiter plates may conveniently be utilized as the solid phase. The anchored component may be immobilized by non-covalent or covalent attachments. Non-covalent attachment may be accomplished by simply coating the solid surface with a solution of the protein and drying. Alternatively, an immobilized antibody, preferably a monoclonal antibody, specific for the peptide or protein to be immobilized may be used to anchor the peptide or protein to the solid surface. The surfaces may be prepared in advance and stored.

In order to conduct the assay, the nonimmobilized component is added to the coated surface containing the anchored component. After the reaction is complete, unreacted components are removed (*e.g.*, by washing) under conditions such that any complexes formed will remain immobilized on the solid surface. The detection of complexes anchored on the solid surface can be accomplished in a number of ways. Where the previously nonimmobilized component is pre-labeled, the detection of label immobilized on the surface indicates that complexes were formed. Where the previously nonimmobilized component is not pre-labeled, an indirect label can be used to detect complexes anchored on the surface; *e.g.*, using a labeled antibody specific for the previously nonimmobilized component (the antibody, in turn, may be directly labeled or indirectly labeled with a labeled anti-Ig antibody).

Alternatively, a reaction can be conducted in a liquid phase, the reaction products separated from unreacted components, and complexes detected; *e.g.*, using an immobilized antibody specific for one component of complexes formed, like, for example, the peptide or protein of interest of the current invention or the test compound to anchor any complexes formed in solution, and a labeled antibody specific for the other component of the possible complex to detect anchored complexes.

5.6.2 ASSAYS FOR INTRACELLULAR PROTEINS THAT INTERACT WITH THE PEPTIDES AND PROTEINS OF THE CURRENT INVENTION

Any method suitable for detecting protein-protein interactions may be employed for identifying intracellular peptides and proteins that interact with peptides and proteins of the current invention. Among the traditional methods which may be employed are co-immunoprecipitation, crosslinking and co-purification through gradients or

chromatographic columns of cell lysates or proteins obtained from cell lysates and the peptides and proteins of the current invention to identify proteins in the lysate that interact with those peptides and proteins of the current invention. For these assays, the peptides and proteins of the current invention may be used in full length, or in truncated or modified forms or as fusion-proteins. Similarly, the component may be a complex of two or more of the peptides and proteins of the current invention. Once isolated, such an intracellular protein can be identified and can, in turn, be used in conjunction with standard techniques to identify proteins with which it interacts. For example, at least a portion of the amino acid sequence of an intracellular protein which interacts with a peptide or protein of the current invention, can be ascertained using techniques well known to those of skill in the art, such as via the Edman degradation technique. (See, *e.g.*, Creighton, 1983, "Proteins: Structures and Molecular Principles", W.H. Freeman & Co., N.Y., pp.34-49). The amino acid sequence obtained may be used as a guide for the generation of oligonucleotide mixtures that can be used to screen for gene sequences encoding such intracellular proteins. Screening may be accomplished, for example, by standard hybridization or PCR techniques. Techniques for the generation of oligonucleotide mixtures and the screening are well-known. (See, *e.g.*, Ausubel, supra., and PCR Protocols: A Guide to Methods and Applications, 1990, Innis, M. *et al.*, eds. Academic Press, Inc., New York).

Additionally, methods may be employed which result in the simultaneous identification of genes which encode the intracellular proteins interacting with peptides and proteins of the current invention. These methods include, for example, probing expression libraries, in a manner similar to the well known technique of antibody probing of ëgt11 libraries, using a labeled form of a peptide or protein of the current invention, or a fusion protein, *e.g.*, a peptide or protein at least partially encoded by a GTS of the present invention fused to a marker (*e.g.*, an enzyme, fluor, luminescent protein, or dye), or an Ig-Fc domain.

One method that detects protein interactions *in vivo*, the two-hybrid system, is described in detail for illustration only and not by way of limitation. One version of this system has been described (Chien *et al.*, 1991, Proc. Natl. Acad. Sci. USA, 88:9578-9582) and is commercially available from Clontech (Palo Alto, CA).

Briefly, utilizing such a system, plasmids are constructed that encode two hybrid proteins: one plasmid consists of nucleotides encoding the DNA-binding domain of a transcription activator protein fused to a nucleotide sequence of the current invention encoding a peptide or protein of the current invention, a modified or truncated form or a fusion protein, and the other plasmid consists of nucleotides encoding the transcription activator protein's activation domain fused to a cDNA encoding an unknown protein which has been recombined into this plasmid as part of a cDNA library. The DNA-binding domain fusion plasmid and the cDNA library are transformed into a strain of the yeast *Saccharomyces cerevisiae* that contains a reporter gene (*e.g.*, HBS or *lacZ*) whose regulatory region contains the transcription activator's binding site. Either hybrid protein alone cannot activate transcription of the reporter gene; the DNA-binding domain hybrid cannot because it does not provide activation function, and the activation domain hybrid cannot because it cannot localize to the activator's binding sites. Interaction of the two hybrid proteins reconstitutes the functional activator protein and results in expression of the reporter gene, which is detected by an assay for the reporter gene product.

The two-hybrid system or related methodology may be used to screen activation domain libraries for proteins that interact with the "bait" gene product. By way of example, and not by way of limitation, a peptide or protein of the current invention may be used as the bait gene product. Total genomic or cDNA sequences are fused to the DNA encoding an activation domain. This library and a plasmid encoding a hybrid of a bait gene product of the current invention fused to the DNA-binding domain are cotransformed into a yeast reporter strain, and the resulting transformants are screened for those that express the reporter gene. For example, and not by way of limitation, a bait gene sequence of the current invention can be cloned into a vector such that it is translationally fused to the DNA encoding the DNA-binding domain of the GAL4 protein. These colonies are purified and the library plasmids responsible for reporter gene expression are isolated. DNA sequencing is then used to identify the proteins encoded by the library plasmids.

A cDNA library of the cell line from which proteins that interact with bait gene product of the current invention are to be detected can be made using methods routinely practiced in the art. According to the particular system described herein, for example, the

cDNA fragments can be inserted into a vector such that they are translationally fused to the transcriptional activation domain of GAL4. This library can be co-transfected along with the bait gene-GAL4 fusion plasmid into a yeast strain which contains a lacZ gene driven by a promoter which contains GAL4 activation sequence. A cDNA encoded protein, fused to GAL4 transcriptional activation domain, that interacts with bait gene product will reconstitute an active GAL4 protein and thereby drive expression of the HIS3 gene. Colonies which express HIS3 can be detected by their growth on petri dishes containing semi-solid agar based media lacking histidine. The cDNA can then be purified from these strains, and used to produce and isolate the bait gene-interacting protein using techniques routinely practiced in the art.

5.6.3 ASSAYS FOR COMPOUNDS THAT INTERFERE WITH INTERACTIONS OF THE PEPTIDES AND PROTEINS OF THE CURRENT INVENTION WITH INTRACELLULAR MACROMOLECULES

The macromolecules that interact with the peptides and proteins of the current invention are referred to, for purposes of this discussion, as "binding partners". These binding partners are likely to be involved in catalytic reactions or signal transduction pathways, and therefore, in the role of the peptides and proteins of the current invention in development and cell differentiation. It is also desirable to identify compounds that interfere with or disrupt the interaction of such binding partners with the peptides and proteins of the current invention which may be useful in regulating the activity of the peptides and proteins of the current invention and thus control development and cell differentiation disorders associated with the activity of the peptides and proteins of the current invention.

The basic principle of the assay systems used to identify compounds that interfere with the interaction between the peptides and proteins of the current invention and its binding partner or partners involves preparing a reaction mixture containing the peptides or proteins of the current invention of interest, modified or truncated version thereof, or fusion proteins thereof as described above, and the binding partner under conditions and for a time sufficient to allow the two to interact and bind, thus forming a complex. In order to test a compound for inhibitory activity, the reaction mixture is prepared in the presence and absence of the test

compound. The test compound may be initially included in the reaction mixture, or may be added at a time subsequent to the addition of the peptide or protein of the current invention and its binding partner. Control reaction mixtures are incubated without the test compound or with a placebo. The formation of any complexes between the peptide or protein of the current invention and the binding partner is then detected. The formation of a complex in the control reaction, but not in the reaction mixture containing the test compound, indicates that the compound interferes with the interaction of the peptide or protein at least partially encoded by a GTS of the present invention and the interactive binding partner. Additionally, complex formation within reaction mixtures containing the test compound and normal peptide or protein of the current invention may also be compared to complex formation within reaction mixtures containing the test compound and a mutant peptide or protein of the current invention. This comparison can be important in those cases wherein it is desirable to identify compounds that disrupt interactions of mutant but not normal forms of a peptide or protein of the current invention.

The assay for compounds that interfere with the interaction of a peptide or protein of the current invention and binding partners can be conducted in a heterogeneous or homogeneous format. Heterogeneous assays involve anchoring either the peptide or protein of the current invention or the binding partner onto a solid phase and detecting complexes anchored on the solid phase at the end of the reaction. In homogeneous assays, the entire reaction is carried out in a liquid phase. In either approach, the order of addition of reactants can be varied to obtain different information about the compounds being tested. For example, test compounds that interfere with the interaction by competition can be identified by conducting the reaction in the presence of the test substance; *i.e.*, by adding the test substance to the reaction mixture prior to or simultaneously with the peptide or protein of the current invention and interactive binding partner. Alternatively, test compounds that disrupt preformed complexes, *e.g.* compounds with higher binding constants that displace one of the components from the complex, can be tested by adding the test compound to the reaction mixture after complexes have been formed. The various formats are described briefly below.

In a heterogeneous assay system, either the peptide or protein of the current invention or the interactive binding partner, is anchored onto a solid surface, while the non-anchored

species is labeled either directly or indirectly. In practice, microtiter plates are conveniently utilized. The anchored species may be immobilized by non-covalent or covalent attachments. Non-covalent attachment may be accomplished simply by coating the solid surface with a solution of the peptide or protein of the current invention or binding partner and drying. Alternatively, an immobilized antibody specific for the species to be anchored may be used to anchor the species to the solid surface. The surfaces may be prepared in advance and stored.

In order to conduct the assay, the partner of the immobilized species is exposed to the coated surface with or without the test compound. After the reaction is complete, unreacted components are removed (*e.g.*, by washing) and any complexes formed will remain immobilized on the solid surface. The detection of complexes anchored on the solid surface can be accomplished in a number of ways. Where the non-immobilized species is pre-labeled, the detection of label immobilized on the surface indicates that complexes were formed. Where the non-immobilized species is not pre-labeled, an indirect label can be used to detect complexes anchored on the surface; *e.g.*, using a labeled antibody specific for the initially non-immobilized species (the antibody, in turn, may be directly labeled or indirectly labeled with a labeled anti-Ig antibody). Depending upon the order of addition of reaction components, test compounds which inhibit complex formation or which disrupt preformed complexes can be detected.

Alternatively, the reaction can be conducted in a liquid phase in the presence or absence of the test compound, the reaction products separated from unreacted components, and complexes detected; *e.g.*, using an immobilized antibody specific for one of the binding components to anchor any complexes formed in solution, and a labeled antibody specific for the other partner to detect anchored complexes. Again, depending upon the order of addition of reactants to the liquid phase, test compounds which inhibit complex or which disrupt preformed complexes can be identified.

In an alternate embodiment of the invention, a homogeneous assay can be used. In this approach, a preformed complex of the peptide or protein of the current invention and the interactive binding partner is prepared in which either the peptide or protein of the current invention or its binding partner is labeled, but the signal generated by the label is quenched due to formation of the complex (see, *e.g.*, U.S. Patent No. 4,109,496 by Rubenstein which

utilizes this approach for immunoassays). The addition of a test substance that competes with and displaces one of the species from the preformed complex will result in the generation of a signal above background. In this way, test substances which disrupt peptide or protein of the current invention/intracellular binding partner interaction can be identified.

In a particular embodiment, a peptide or protein of the current invention can be prepared for immobilization. For example, the peptide or protein of the current invention or a fragment thereof can be fused to a glutathione-S-transferase (GST) gene using a fusion vector, such as pGEX-5X-1, in such a manner that its binding activity is maintained in the resulting fusion protein. The interactive binding partner can be purified and used to raise a monoclonal antibody, using methods routinely practiced in the art and described above. This antibody can be labeled with the radioactive isotope ^{125}I, for example, by methods routinely practiced in the art. In a heterogeneous assay, *e.g.*, the GST-peptide or protein of the current invention fusion protein can be anchored to glutathione-agarose beads. The interactive binding partner can then be added in the presence or absence of the test compound in a manner that allows interaction and binding to occur. At the end of the reaction period, unbound material can be washed away, and the labeled monoclonal antibody can be added to the system and allowed to bind to the complexed components. The interaction between the peptide or protein of the current invention and the interactive binding partner can be detected by measuring the amount of radioactivity that remains associated with the glutathione-agarose beads. A successful inhibition of the interaction by the test compound will result in a decrease in measured radioactivity.

Alternatively, the GST-peptide or protein of the current invention fusion protein and the interactive binding partner can be mixed together in liquid in the absence of the solid glutathione-agarose beads. The test compound can be added either during or after the species are allowed to interact. This mixture can then be added to the glutathione-agarose beads and unbound material is washed away. Again the extent of inhibition of the peptide or protein of the current invention/binding partner interaction can be detected by adding the labeled antibody and measuring the radioactivity associated with the beads.

In another embodiment of the invention, these same techniques can be employed using peptide fragments that correspond to the binding domains of a peptide or protein of the

current invention and/or the interactive or binding partner (in cases where the binding partner is a protein) in place of one or both of the full length proteins. Any number of methods routinely practiced in the art can be used to identify and isolate the binding sites. These methods include, but are not limited to, mutagenesis of the gene encoding one of the proteins and screening for disruption of binding in a co-immunoprecipitation assay. Compensating mutations in the gene encoding the second species in the complex can then be selected. Sequence analysis of the genes encoding the respective proteins will reveal the mutations that correspond to the region of the protein involved in interactive binding. Alternatively, one protein can be anchored to a solid surface using methods described above, and allowed to interact with and bind to its labeled binding partner, which has been treated with a proteolytic enzyme, such as trypsin. After washing, a short, labeled peptide comprising the binding domain may remain associated with the solid material, which can be isolated and identified by amino acid sequencing. Also, once the gene coding for the intracellular binding partner is obtained, short gene segments can be engineered to express peptide fragments of the protein, which can then be tested for binding activity and purified or synthesized.

For example, and not by way of limitation, a peptide or protein of the current invention can be anchored to a solid material as described, above, by making a GST-peptide or protein of the current invention fusion protein and allowing it to bind to glutathione agarose beads. The interactive binding partner can be labeled with a radioactive isotope, such as ^{35}S, and cleaved with a proteolytic enzyme such as trypsin. Cleavage products can then be added to the anchored GST-peptide or protein of the current invention fusion protein and allowed to bind. After washing away unbound peptides, labeled bound material, representing the intracellular binding partner binding domain, can be eluted, purified, and analyzed for amino acid sequence by well-known methods. Peptides so identified can be produced synthetically or fused to appropriate facilitative proteins using recombinant DNA technology.

5.6.4 ASSAYS FOR IDENTIFICATION OF COMPOUNDS THAT AMELIORATE DISORDERS AFFECTING DEVELOPMENT AND CELL DIFFERENTIATION

Compounds including, but not limited to, binding compounds identified via assay techniques such as those described above, can be tested for the ability to ameliorate

development and cell differentiation disorder symptoms. The assays described above can identify compounds which affect the activity of peptides and proteins of the current invention (*e.g.*, compounds that bind to the peptides and proteins of the current invention, inhibit binding of their natural ligands, and compounds that bind to a natural ligand of the peptides and proteins of the current invention and neutralize the ligand activity); or compounds that affect the activity of genes encoding peptides and proteins of the current invention (by affecting the expression of those genes, including molecules, *e.g.*, proteins or small organic molecules, that affect or interfere with splicing events so that expression of the genes of interest can be modulated). However, it should be noted that the assays described herein can also identify compounds that modulate signal transduction or catalytic events that the peptides and proteins of the current invention are involved in. The identification and use of such compounds which affect a step in, for example, signal transduction pathways or catalytic events in which any of the peptides and proteins of the current invention are involved in, may modulate the effect of the peptides and proteins of the current invention on developmental or cell differentiation disorders. Such identification and use of such compounds are within the scope of the invention. Such compounds can be used as part of a therapeutic method for the treatment of developmental and cell differentiation disorders.

The invention encompasses cell-based and animal model-based assays for the identification of compounds exhibiting such an ability to ameliorate developmental and cell differentiation disorder symptoms. Such cell-based assay systems can also be used as the standard to assay for purity and potency of the natural ligand, catalytic subunit, including recombinantly or synthetically produced catalytic subunit and catalytic subunit mutants.

Cell-based systems can be used to identify compounds which may act to ameliorate developmental or cell differentiation disorder symptoms. Such cell systems can include, for example, recombinant or non-recombinant cells, such as cell lines, which express the gene encoding the peptide or protein of interest of the current invention. For example ES cells, or cell lines derived from ES cells can be used. In addition, expression host cells (*e.g.*, COS cells, CHO cells, fibroblasts, Sf9 cells) genetically engineered to express a functional peptide or protein of the current invention in addition to factors necessary for the peptide or protein of

the current invention to fulfil its physiological role of, for example, signal transduction or catalyses, can be used as an end point in the assay.

In utilizing such cell systems, cells may be exposed to a compound suspected of exhibiting an ability to ameliorate developmental or cell differentiation disorder symptoms, at a sufficient concentration and for a time sufficient to elicit such an amelioration of such disorder symptoms in the exposed cells. After exposure, the cells can be assayed to measure alterations in the expression of the gene encoding the peptide or protein of interest of the current invention, *e.g.*, by assaying cell lysates for the appropriate mRNA transcripts (*e.g.*, by Northern analysis) or for expression of the peptide or protein of interest of the current invention in the cell; compounds which regulate or modulate expression of the gene encoding the peptide or protein of interest of the current invention are valuable candidates as therapeutics. Alternatively, the cells are examined to determine whether one or more developmental or cell differentiation disorder-like cellular phenotypes has been altered to resemble a more normal or more wild type phenotype, or a phenotype more likely to produce a lower incidence or severity of disorder symptoms. Still further, the expression and/or activity of components of pathways or functionally or physiologically connected peptides or proteins of which the peptide or protein of interest of the current invention is a part, can be assayed.

For example, after exposure of the cells, cell lysates can be assayed for the presence of increased levels of the test compound as compared to lysates derived from unexposed control cells. The ability of a test compound to inhibit production of the assay compound such systems indicates that the test compound inhibits signal transduction initiated by the peptide or protein of interest of the current invention. Finally, a change in cellular morphology of intact cells may be assayed using techniques well known to those of skill in the art.

In addition, animal-based development or cell differentiation disorder systems, which may include, for example, mice, may be used to identify compounds capable of ameliorating development or cell differentiation disorder-like symptoms. Such animal models may be used as test systems for the identification of drugs, pharmaceuticals, therapies and interventions which may be effective in treating such disorders. For example, animal models may be exposed to a compound, suspected of exhibiting an ability to ameliorate development

or cell differentiation disorder symptoms, at a sufficient concentration and for a time sufficient to elicit such an amelioration of development and/or cell differentiation disorder symptoms in the exposed animals. The response of the animals to the exposure may be monitored by assessing the reversal of disorders associated with development and/or cell differentiation disorders. With regard to intervention, any treatments which reverse any aspect of development or cell differentiation disorder-like symptoms should be considered as candidates for human development and/or cell differentiation disorder therapeutic intervention. Dosages of test agents may be determined by deriving dose-response curves, as discussed below.

5.7 THE TREATMENT OF DISORDERS ASSOCIATED WITH STIMULATION OF PEPTIDES AND PROTEINS OF THE CURRENT INVENTION

The invention also encompasses methods and compositions for modifying development and cell differentiation and treating development and cell differentiation disorders. For example, one may decrease the level of expression of one or more genes of the current invention, and/or downregulate activity of one or more of the peptides or proteins of interest of the current invention. Thereby, the response of cells, like, for example, ES cells, to factors which activate the physiological responses that enhance the pathological processes leading to developmental and cell differentiation disorders may be reduced and the symptoms ameliorated. Conversely, the response of cells, like, for example, ES cells, to physiological stimuli involving any of the peptides or proteins of the current invention and necessary for proper developmental and cell differentiation processes may be augmented by increasing the activity of one or several of the peptides or proteins of interest of the current invention. Different approaches are discussed below.

5.7.1 INHIBITION OF PEPTIDES AND PROTEINS OF THE CURRENT INVENTION TO REDUCE DEVELOPMENT AND CELL DIFFERENTIATION DISORDERS

Any method which neutralizes the catalytic or signal transduction activity of the peptides and proteins of the current invention or which inhibits expression of the genes

encoding peptides and proteins (either transcription or translation) can be used to reduce symptoms associated with developmental and cell differentiation disorders.

In one embodiment, immuno therapy can be designed to reduce the level of endogenous gene expression for the peptides and proteins of the current invention, *e.g.*, using antisense or ribozyme approaches to inhibit or prevent translation of mRNA transcripts; triple helix approaches to inhibit transcription of the genes; or targeted homologous recombination to inactivate or "knock out" the genes or its endogenous promoter.

Antisense approaches involve the design of oligonucleotides (either DNA or RNA) that are complementary to mRNA specific for peptides and proteins of interest of the current invention. The antisense oligonucleotides will bind to the complementary mRNA transcripts and prevent translation. Absolute complementarity, although preferred, is not required. A sequence "complementary" to a portion of an RNA, as referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex. In the case of double-stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the longer the hybridizing nucleic acid, the more base mismatches with an RNA it may contain and still form a stable duplex (or triplex, as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

Oligonucleotides that are complementary to the 5' end of the message, *e.g.*, the 5' untranslated sequence up to and including the AUG initiation codon, should work most efficiently at inhibiting translation. However, sequences complementary to the 3' untranslated sequences of mRNAs have recently shown to be effective at inhibiting translation of mRNAs as well. See generally, Wagner, R., 1994, Nature *372*:333-335. Thus, oligonucleotides complementary to either the 5'- or 3'- non- translated, non-coding regions of the mRNAs specific for the peptides and proteins of the current invention could be used in an antisense approach to inhibit translation of those endogenous mRNAs. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. Antisense oligonucleotides complementary to mRNA coding regions

are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5'-, 3'- or coding region of an mRNA, antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50 nucleotides in length. In specific aspects the oligonucleotide is at least 10 nucleotides, at least 17 nucleotides, at least 25 nucleotides or at least 50 nucleotides.

Regardless of the choice of target sequence, it is preferred that *in vitro* studies are first performed to quantitate the ability of the antisense oligonucleotide to inhibit gene expression. It is preferred that these studies utilize controls that distinguish between antisense gene inhibition and nonspecific biological effects of oligonucleotides. It is also preferred that these studies compare levels of the target RNA or protein with that of an internal control RNA or protein. Additionally, it is envisioned that results obtained using the antisense oligonucleotide are compared with those obtained using a control oligonucleotide. It is preferred that the control oligonucleotide is of approximately the same length as the test oligonucleotide and that the nucleotide sequence of the oligonucleotide differs from the antisense sequence no more than is necessary to prevent specific hybridization to the target sequence.

The oligonucleotides can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotide may include other appended groups such as peptides (*e.g.*, for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, e.g., Letsinger *et al.*, 1989, Proc. Natl. Acad. Sci. U.S.A. *86*:6553-6556; Lemaitre *et al.*, 1987, Proc. Natl. Acad. Sci. *84*:648-652; PCT Publication No. WO88/09810, published December 15, 1988), or hybridization-triggered cleavage agents. (See, e.g., Krol *et al.*, 1988, BioTechniques *6*:958-976) or intercalating agents. (See, *e.g.*, Zon, 1988, Pharm. Res. 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, *e.g.*, a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The antisense oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to, 5-fluorouracil, 5-bromouracil,

5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The antisense oligonucleotide may also comprise at least one modified sugar moiety selected from the group including, but not limited to, arabinose, 2-fluoroarabinose, xylulose, and hexose.

In another embodiment, the antisense oligonucleotide comprises at least one modified phosphate backbone selected from the group consisting of a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

In yet another embodiment, the antisense oligonucleotide is an alpha-anomeric oligonucleotide. An alpha-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual alpha-units, the strands run parallel to each other (Gautier *et al.*, 1987, Nucl. Acids Res. *15*:6625-6641). The oligonucleotide is a 2'-0-methylribonucleotide (Inoue *et al.*, 1987, Nucl. Acids Res. *15*:6131-6148), or a chimeric RNA-DNA analogue (Inoue *et al.*, 1987, FEBS Lett. *215*:327-330).

Oligonucleotides of the invention may be synthesized by standard methods known in the art, *e.g.* by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein *et al.*, 1988, Nucl. Acids Res. *16*:3209. Methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin *et al.*, 1988, Proc. Natl. Acad. Sci. U.S.A. *85*:7448-7451).

While antisense nucleotides complementary to the coding region sequence specific for the peptides and proteins of the current invention could be used, those complementary to the transcribed untranslated region are most preferred.

The antisense molecules should be delivered to cells which express the peptides and proteins of interest of the current invention *in vivo*, like, for example, ES cells. A number of methods have been developed for delivering antisense DNA or RNA to cells; *e.g.*, antisense molecules can be injected directly into the tissue or cell derivation site, or modified antisense molecules, designed to target the desired cells (*e.g.*, antisense linked to peptides or antibodies that specifically bind receptors or antigens expressed on the target cell surface) can be administered systemically.

However, it is often difficult to achieve intracellular concentrations of antisense molecules that are sufficient to suppress translation of endogenous mRNAs. Therefore a preferred approach utilizes a recombinant DNA construct in which the antisense oligonucleotide is placed under the control of a strong pol III or pol II promoter. The use of such a construct to transfect target cells in the patient will result in the transcription of sufficient amounts of single stranded RNAs that will form complementary base pairs with the endogenous transcripts specific for the peptides and proteins of interest of the current invention and thereby prevent translation of the respective mRNAs. For example, a vector can be introduced *in vivo* such that it is taken up by a cell and directs the transcription of an antisense RNA. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art, used for replication and expression in mammalian cells. Expression of the sequence encoding the antisense RNA can be by any promoter known in the art to act in mammalian, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to: the SV40 early promoter region (Bernoist and Chambon, 1981, Nature 290:304-310), the promoter contained in the 3′ long terminal repeat of Rous sarcoma virus (Yamamoto *et al.*, 1980, Cell 22:787-797), the herpes thymidine kinase promoter (Wagner *et al.*, 1981, Proc. Natl. Acad. Sci. U.S.A. 78:1441-1445), the regulatory sequences of the metallothionein gene (Brinster *et al.*,

1982, Nature 296:39-42), etc. Any type of plasmid, cosmid, YAC or viral vector can be used to prepare the recombinant DNA construct which can be introduced directly into the tissue or cell derivation site; *e.g.*, the bone marrow. Alternatively, viral vectors can be used which selectively infect the desired tissue or cell type; (*e.g.*, viruses which infect cells of hematopoietic lineage), in which case administration may be accomplished by another route (*e.g.*, systemically).

Ribozyme molecules designed to catalytically cleave mRNA transcripts specific for the peptides and proteins of interest of the current invention can also be used to prevent translation of the mRNAs of interest and expression of the peptides and proteins encoded by those mRNAs. (See, *e.g.*, PCT International Publication WO90/11364, published October 4, 1990; Sarver *et al.*, 1990, Science 247:1222-1225). While ribozymes that cleave mRNA at site specific recognition sequences can be used to destroy mRNAs, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Haseloff and Gerlach, 1988, Nature, *334*:585-591. Preferably the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the mRNA of interest; *i.e.*, to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.

The ribozymes of the present invention also include RNA endoribonucleases (hereinafter "Cech-type ribozymes") such as the one which occurs naturally in Tetrahymena Thermophila (known as the IVS, or L-19 IVS RNA) and which has been extensively described by Thomas Cech and collaborators (Zaug *et al.*, 1984, Science, *224*:574-578; Zaug and Cech, 1986, Science, *231*:470-475; Zaug *et al.*, 1986, Nature, *324*:429-433; published International Patent Application No. WO 88/04300 by University Patents Inc.; Been and Cech, 1986, Cell, *47*:207-216). The Cech-type ribozymes have an eight base pair active site which hybridizes to a target RNA sequence where after cleavage of the target RNA takes place. The invention encompasses those Cech-type ribozymes which target eight base-pair

active site sequences that are present in the mRNAs specific for the peptides and proteins of interest of the current invention.

As in the antisense approach, the ribozymes can be composed of modified oligonucleotides (*e.g.* for improved stability, targeting, etc.) and should be delivered to cells which express the peptides and proteins of interest of the current invention *in vivo*, like, for example, ES cells. A preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the ribozyme to destroy the endogenous messages specific for the peptides and proteins of interest of the current invention and inhibit translation. Because ribozymes unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency.

Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene of interest specific for a peptide or protein of the current invention or its promoter using targeted homologous recombination. (*e.g.*, see Smithies *et al.*, 1985, Nature *317*:230-234; Thomas & Capecchi, 1987, Cell *51*:503-512; Thompson *et al.*, 1989 Cell *5*:313-321; each of which is incorporated by reference herein in its entirety). For example, a mutant, non-functional peptide or protein of interest of the current invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous gene encoding said peptide or protein of interest of the current invention (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express said peptide or protein of interest of the current invention *in vivo*. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted endogenous gene. Such approaches are particularly suited in the agricultural field where modifications to ES cells can be used to generate animal offspring with an inactive copy of a gene encoding a peptide or protein of interest of the current invention (*e.g.*, see Thomas & Capecchi 1987 and Thompson 1989, supra). However this approach can be adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors.

Alternatively, endogenous expression of a gene of interest can be reduced by targeting deoxyribonucleotide sequences complementary to the regulatory region of said gene (*i.e.*, the promoter and/or enhancers) to form triple helical structures that prevent transcription of the gene of interest in target cells in the body. (See generally, Helene, C. 1991, Anticancer Drug Des., *6(6)*:569-84; Helene, C. *et al.*, 1992, Ann, N.Y. Acad. Sci., *660*:27-36; and Maher, L.J., 1992, Bioassays *14(12)*:807-15).

In yet another embodiment of the invention, the activity of a peptide or protein of interest of the current invention can be reduced using a "dominant negative" approach. A dominant negative approach takes advantage of the interaction of the peptides or proteins of interest with other peptides or proteins to form complexes, the formation of which is a prerequisite for the peptide or protein of interest of the current invention to exert its physiological activity. To this end, constructs which encode a defective form of the peptide or protein of interest of the current invention can be used in gene therapy approaches to diminish the activity of said peptide or protein of interest in appropriate target cells. Alternatively, targeted homologous recombination can be utilized to introduce such deletions or mutations into the subject's endogenous gene encoding the peptide or protein of interest of the current invention in the appropriate tissue. The engineered cells will express non-functional copies of the peptide or protein of interest of the current invention, thereby downregulating its activity *in vivo*. Such engineered cells should demonstrate a diminished response to physiological stimuli of the activity of the affected peptide or protein of interest of the current invention, resulting in reduction of the development or cell differentiation disorder phenotype.

5.7.2 RESTORATION OR INCREASE IN EXPRESSION OR ACTIVITY OF A PEPTIDE OR PROTEIN OF THE CURRENT INVENTION TO PROMOTE DEVELOPMENT OR CELL DIFFERENTIATION

With respect to an increase in the level of normal gene expression and/or gene product activity specific for any of the peptides and proteins of interest of the current invention, the respective nucleic acid sequences can be utilized for the treatment of development and cell differentiation disorders. Where the cause of the development or cell differentiation

dysfunction is a defective peptide or protein of the current invention, treatment can be administered, for example, in the form of gene delivery or gene therapy. Specifically, one or more copies of a normal gene or a portion of the gene that directs the production of a gene product exhibiting normal function of the appropriate peptide or protein of the current invention, may be inserted into the appropriate cells within a patient or animal subject, optionally using suitable vectors. Recombinant retroviruses have been widely used in gene transfer or gene delivery experiments and even human clinical trials (see generally, Mulligan, R.C., Chapter 8, In: Experimental Manipulation of Gene Expression, Academic Press, pp. 155-173 (1983); Coffin, J., In: RNA Tumor Viruses, Weiss, R. *et al.* (eds.), Cold Spring Harbor Laboratory, Vol. 2, pp. 36-38 (1985). Other eucaryotic viruses which have been used as vectors to transduce mammalian cells include adenovirus, papilloma virus, herpes virus, adeno-associated virus, vaccinia virus, rabies virus, and the like (See generally, Sambrook *et al.*, Molecular Cloning, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, Vol. 3:16.1-16.89 (1989). Alternatively, cationic or other lipids may be employed to deliver polynucleotides comprising (or including) the described GTS sequences to patients. Additionally, naked DNA comprising one or more GTS sequences, optionally modified by the addition of one or more of, in operable combination and orientation, a promoter, an enhancer, a ribosome entry or ribosome binding site, and/or an in-frame translation initiation codon can be employed to deliver GTSs to a patient. Another use of the above constructs includes "naked" DNA vaccines that can be introduced *in vivo* alone, or in conjunction with excipients, or microcarrier spheres, nanoparticles or other supporting or dosaging compounds or molecules.

The gene replacement/delivery therapies described above should be capable of delivering gene sequences to the cell types within patients which express the peptide or protein of interest of the current invention. Alternatively, targeted homologous recombination can be utilized to correct the defective endogenous gene in the appropriate cell type. In animals, targeted homologous recombination can be used to correct the defect in ES cells in order to generate offspring with a corrected trait.

Finally, compounds identified in the assays described above that stimulate, enhance, or modify the activity of the peptides and proteins of the current invention can be used to

achieve proper development and cell differentiation. The formulation and mode of administration will depend upon the physico-chemical properties of the compound.

5.8 PHARMACEUTICAL PREPARATIONS AND METHODS OF ADMINISTRATION

Compounds that are determined to affect gene expression of the peptides and proteins of the current invention, comprise nucleotide sequence information that is at least partially first disclosed in the Sequence Listing (*i.e.*, sequences used in antisense, gene therapy, dsRNA, or ribozyme applications), or the interaction of such peptides and proteins with any of their binding partners, can be administered to a patient at therapeutically effective doses to treat or ameliorate development and cell differentiation disorders. A therapeutically effective dose refers to that amount of the compound sufficient to result in any amelioration or retardation of disease symptoms, or development and cell differentiation or proliferation disorders.

5.8.1 EFFECTIVE DOSE

Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD_{50}/ED_{50}. Compounds which exhibit large therapeutic indices are preferred. While compounds that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such compounds to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the

invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC_{50} (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

When the therapeutic treatment of disease is contemplated, the appropriate dosage may also be determined using animal studies to determine the maximal tolerable dose, or MTD, of a bioactive agent per kilogram weight of the test subject. In general, at least one animal species tested is mammalian. Those skilled in the art regularly extrapolate doses for efficacy and avoiding toxicity to other species, including human. Before human studies of efficacy are undertaken, Phase I clinical studies in normal subjects help establish safe doses.

Additionally, the bioactive agent may be complexed with a variety of well established compounds or structures that, for instance, enhance the stability of the bioactive agent, or otherwise enhance its pharmacological properties (e.g., increase *in vivo* half-life, reduce toxicity, etc.).

The above therapeutic agents will be administered by any number of methods known to those of ordinary skill in the art including, but not limited to, administration by inhalation; by subcutaneous (sub-q), intravenous (I.V.), intraperitoneal (I.P.), intramuscular (I.M.), or intrathecal injection; or as a topically applied agent (transderm, ointments, creams, salves, eye drops, and the like).

5.8.2 FORMULATIONS AND USE

Pharmaceutical compositions for use in accordance with the present invention may be formulated in conventional manner using one or more physiologically acceptable carriers or excipients.

Thus, the compounds and their physiologically acceptable salts and solvates may be formulated for administration by inhalation or insufflation (either through the mouth or the nose) or oral, buccal, parenteral or rectal administration.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (*e.g.*, pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (*e.g.*, lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (*e.g.*, magnesium stearate, talc or silica); disintegrants (*e.g.*, potato starch or sodium starch glycolate); or wetting agents (*e.g.*, sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (*e.g.*, sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (*e.g.*, lecithin or acacia); non-aqueous vehicles (*e.g.*, almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (*e.g.*, methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavoring, coloring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of *e.g.* gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit

dosage form, *e.g.*, in ampules or in multi-dose containers, with an added preservative. The compositions

may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

The compounds may also be formulated as compositions for rectal administration such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt. The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may, for example, comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration.

The examples below are provided to illustrate the subject invention. These examples are provided by way of illustration and are not included for the purpose of limiting the invention in any way whatsoever.

6. EXAMPLES

6.1 CONSTRUCTION OF TRAPPED cDNA LIBRARIES

The GTSs represented in SEQ ID NOS:9-503 were generated using normalized cDNA libraries produced as described in U.S. application Ser. No. 60/095,989, filed August 10, 1998 entitled "Construction of Normalized cDNA Libraries From Animal Cells" (also identified as attorney docket no. 8535-021-888), by Nehls *et al.*, the disclosure of which is herein incorporated by reference in its entirety.

Figure 1A provides a representative illustration of the retroviral vector used to produce the described polynucleotides. In brief, pools of modified human PA-1 teratocarcinoma cells (*e.g.*, PA-2, PA-1 that has been transfected to express the murine ecotropic retrovirus receptor) were typically infected at an m.o.i. between about 0.01 and about 0.1 (although much higher m.o.i.'s such as 1 to more than 10 could have been used). Figure 1B schematically shows how the target cell genomic locus is presumably mutated by the integration of the retroviral construct into intronic sequences of the cellular gene. The integrated retrovirus results in the generation of two chimeric transcripts. As illustrated in Figure 1C, the first chimeric transcript is a fusion between the coding region of the resistance marker (*neo* was used to produce the presently described GTSs) carried within the transgenic construct and the downstream exon(s) from the cellular gene. A mature transcript is generated when the indicated splice donor (SD) and splice acceptor (SA) sites are spliced. Translation of this fusion transcript produces the protein encoded by the resistance marker and allows for selection of gene trapped target cells, although selection is not required to produce the described polynucleotides.

Another chimeric transcript is shown in Figure 1C. This transcript is a fusion between the first exon of the transgenic construct (EXON1- the first exon of the murine *btk* gene was used as the sequence acquisition component for the described GTSs) and downstream exons from the cellular genome. Unlike the transcript encoding the selectable marker exon, the transcript encoding EXON1 is transcribed under the control of a vector encoded, and hence exogenously added, promoter (such as the PGK promoter), and the corresponding mRNA is generated by splicing between the indicated SD and SA sites. The region encoding the sequence acquisition exon (EXON1) has also been engineered to incorporate a unique sequence that permits the selective enrichment of the fusion transcript using molecular biological methods such as, for example, the polymerase chain reaction (PCR). These sequences serve as unique primer binding sites for EXON1-specific PCR amplification of the transcript and can additionally incorporate one or several rare-cutter endonuclease restriction sites to allow site-specific cloning. These features allow for the efficient and preferential cloning of transgene expressed fusion transcripts from pools of target cells relative to the background of cellularly encoded transcripts.

Based on the unique sequence present in EXON1, that is schematically indicated as a rare-cutter (A) restriction site in Figure 1B, selective cloning of the fusion transcript is achieved as shown in Figure 1D. cDNA was generated by reverse transcribing isolated RNA from pools of cells that have undergone independent gene trap events using, for example, RTT-1 as a deoxyoligonucleotide primer. The 3' end of the RTT-1 primer consisted of a homopolymeric stretch of deoxythymidine residues that bound to the polyadenylated end of the mRNA. At its 5' end, the oligonucleotide contained a sequence that can serve as a binding site for a second and a third primer (GET-2 and GET-2N). In the center, RTT-1 contains the sequence of a second rare-cutter (B) restriction site. Depending on the size of the pool and the transcriptional levels of the fusion transcript, second strand synthesis was carried out either with deoxyoligonucleotide primer BTK-1 using Klenow polymerase or by a polymerase chain reaction (PCR) in the presence of primers BTK-1 and GET-2.

The second strand reaction products that were generated by PCR were digested with restriction endonucleases that recognize their corresponding restriction site (*e.g.*, A and B). Additionally, PCR conditions were suitably modified using a variety of established procedures for enhancing the size of the PCR products. Such methods are described, inter alia, in U.S. Patent No. 5,556,772, and/or the PanVera (Madison, WI) New Technologies for Biomedical Research catalog (1997/98) both of which are herein incorporated by reference.

Prior to cloning, the PCR cDNA fragments were size-selected using conventional methods such as, for example, chromatography, gel-electrophoresis, and the like. Alternatively or in addition to this size selection, the PCR templates could have been previously size selected into separate template pools.

After digestion with suitable restriction enzymes, and size selection as described above, the cleaved cDNAs were directionally cloned into phage vectors (see Figure 1D), although any other cloning vector/vehicle could have been used. Such vectors are generically referred to as gene trapped sequence vectors, or "GTS vectors" in Figure 1D), preferably incorporating a multiple cloning site with restriction sites corresponding to those incorporated into the amplified cDNAs (*e.g.*, *Sfi* I, which allows for directional cloning of the cDNAs). After cloning, the resulting phage were handled as a conventional cDNA library using

standard procedures. Individual colonies and/or plaques were picked and used to generate PCR derived (using the primers indicated below) templates for DNA sequencing reactions.

A more detailed description of the above follows. The *btk* gene trap vector was introduced into human PA-2 cells using standard techniques. In brief, vector/virus containing supernatant from GP+E or AM12 packaging cells was added to approximately 50,000 cells (at an input ratio between about 0.1 and about 0.1 virus/target cell) for between about 16 to about 24 hours, and the cells were subsequently selected with G418 at active concentration of about 400 micrograms/ml for about 10 days. Between about 600 and about 3,000 G418 resistant colonies were subsequently pooled, and subjected to RNA isolation, reverse transcription, PCR, restriction digestion, size selection, and subcloning into lambda phage vectors. Individual phage plaques were directly amplified, purified, and sequenced to obtain the corresponding GTS.

When selection is not used, about 1 x 10^6 cells (PA-2, Hela, HepG2, or Jurkatt cells) per 100 mm dish were plated and infected with AM12 packaged *btk* retrovirus at an m.o.i. of approximately .01. After a 16 h incubation, the cells were washed in PBS and grown in culture media for four days. RNA from each plate was extracted, reverse transcribed, and the resulting cDNA was subject to two rounds of PCR, each for 25 cycles. The resulting PCR products were digested with Sfi and separated by gel electrophoresis. Six size fractions (between about 300 and about 4,000 bp) were recovered and each fraction was ligated into lambdaGT10Sfi arms, *in vitro* packaged, and plated for lysis. Individual plaques were picked from the plates, subject to an additional round of PCR, and subsequently sequenced to obtain the described GTSs. The particulars are described in greater detail below.

Figure 1 shows the chimeric fusion transcript that is formed when the first exon of the transgenic construct (EXON1- the first exon of the murine *btk* gene was used as the sequence acquisition component for the described GTSs) is spliced to downstream exons from the cellular genome. Unlike the transcript encoding the selectable marker exon, the transcript encoding EXON1 is transcribed under the control of a vector encoded, and hence exogenously added, promoter (such as the PGK promoter), and the corresponding mRNA is generated by splicing between the indicated SD and SA sites. The region encoding the sequence acquisition exon (EXON1) has also been engineered to incorporate a unique

sequence that permits the selective enrichment of the fusion transcript using molecular biological methods such as, for example, the polymerase chain reaction (PCR). These sequences serve as unique primer binding sites for EXON1-specific PCR amplification of the transcript and can additionally incorporate one or several rare-cutter endonuclease restriction sites to allow site-specific cloning. These features allow for the efficient and preferential cloning of transgene expressed fusion transcripts from pools of target cells relative to the background of cellularly encoded transcripts.

Based on the unique sequence present in EXON1, that is schematically indicated as a rare-cutter (A) restriction site in Figure 1B, selective cloning of the fusion transcript is achieved as shown in Figure 1D. cDNA was generated by reverse transcribing isolated RNA from pools of cells that have undergone independent gene trap events using, for example, RTT-1 as a deoxyoligonucleotide primer. The 3' end of the RTT-1 primer consisted of a homopolymeric stretch of deoxythymidine residues that bound to the polyadenylated end of the mRNA. At its 5' end, the oligonucleotide contained a sequence that can serve as a binding site for a second and a third primer (GET-2 and GET-2N). In the center, RTT-1 contains the sequence of a second rare-cutter (B) restriction site. Depending on the size of the pool and the transcriptional levels of the fusion transcript, second strand synthesis was carried out either with deoxyoligonucleotide primer BTK-1 using Klenow polymerase or by a polymerase chain reaction (PCR) in the presence of primers BTK-1 and GET-2.

The second strand reaction products that were generated by PCR were digested with restriction endonucleases that recognize their corresponding restriction site (*e.g.*, A and B). Additionally, PCR conditions were suitably modified using a variety of established procedures for enhancing the size of the PCR products. Such methods are described, inter alia, in U.S. Patent No. 5,556,772, and/or the PanVera (Madison, WI) New Technologies for Biomedical Research catalog (1997/98) both of which are herein incorporated by reference.

Prior to cloning, the PCR cDNA fragments were size-selected using conventional methods such as, for example, chromatography, gel-electrophoresis, and the like. Alternatively or in addition to this size selection, the PCR templates could have been previously size selected into separate template pools.

After digestion with suitable restriction enzymes, and size selection as described above, the cleaved cDNAs were directionally cloned into phage vectors (see Figure 1D), although any other cloning vector/vehicle could have been used. Such vectors are generically referred to as gene trapped sequence vectors, or "GTS vectors" in Figure 1D), preferably incorporating a multiple cloning site with restriction sites corresponding to those incorporated into the amplified cDNAs (*e.g.*, *Sfi* I, which allows for directional cloning of the cDNAs). After cloning, the resulting phage were handled as a conventional cDNA library using standard procedures. Individual colonies and/or plaques were picked and used to generate PCR derived (using the primers indicated below) templates for DNA sequencing reactions.

Total cell RNA isolation was conducted using RNAzol (Friendswood, TX, 77546) per the manufacturer's specifications. An RT premix containing 2X First Strand buffer, 100mM Tris-HCl, pH 8.3, 150mM KCl, 6mM $MgCl_2$, 2mM dNTPs, RNAGuard (1.5 units/reaction, Pharmacia), 20mM DTT, RTT-1 primer (3pmol/rxn, GenoSys Biotechnologies, sequence: 5' tggctaggccccaggataggcctcgctggccttttttttttttttt 3', SEQ ID NO:1) and Superscript II enzyme (200 units/rxn, Life Technologies) was added. The plate/tube was transferred to a thermal cycler for the RT reaction (37° C for 5 min. 42° C for 30 min. and 55° C for 10 min).

The cDNA was amplified using two distinct, and preferably nested, stages of PCR. The PCR premix contained: 1.1X MGBII buffer (74 mM Tris pH 8.8, 18.3mM Ammonium Sulfate, 7.4mM $MgCl_2$, 5.5mM 2ME, 0.011% Gelatin), 11.1% DMSO (Sigma), 1.67mM τdNTPS, Taq (5 units/rxn), water and primers. The sequences of the first round primers are: BTK-1 5' gccatggctccggtaggtccagag 3', SEQ ID NO:2 (GET-2, 5' tggctaggccccaggatag 3', SEQ ID NO:3), (about 7 pmol/rxn). The sequences of the second round primers are BTK-4 5' gtccagagatggccatagc 3', SEQ ID NO:4 (GET-2N 5' ccaggataggcctcgctg 3', SEQ ID NO:5), (used at about 20 pmol/rxn). The outer premix was added to an aliquot of cDNA and run for 20 cycles (94° C for 45 sec., 56° C for 60 sec 72° C for 2-4 min). An aliquot of this product was added to the inner premix and cycled at the same temperatures 20 times.

The PCR products of the second amplification series were extracted using phenol/chloroform, chloroform, and isopropanol precipitated in the presence of glycogen/sodium acetate. After centrifugation, the nucleic acid pellets were washed with 70 percent ethanol and were resuspended in TE, pH 8. After digestion with *Sfi* I at 55° C, the

digested products were loaded onto 0.8% agarose gels and size-selected using DEAE membranes as described (Sambrook *et al.*, 1989, *supra*). Generally, six approximate size-fractions (<700 bp, 700-900 bp, 900-1,300 bp, 1,300-1,600 bp, 1,600-2,000 bp, >2,000 bp) were separately ligated into GTS vector arms that were engineered to contain the corresponding *Sfi* I "A" and "B" specific overhangs (*i.e.*, TAG and GCG, respectively). The ligation products were packaged using commercially available lambda packaging extracts (Promega), and plated using *E. coli* strain C600 using conventional procedures (Sambrook *et al.*, 1989, *supra*). Individual plaques were directly picked into 40 microliters of PCR buffer and subjected to 35 cycles of PCR [at 94° C for 45 sec., 56° C for 60 sec 72° C for 1-3 min (depending on the size fraction)] using 12 pmol of the primers SEQ-4, 5' tacagtttttcttgtgaagattg 3', SEQ ID NO:6 and SEQ-5, 5' gggtagtccccacctttttg 3', SEQ ID NO:7, per PCR reaction. The cloned 3' RACE products were purified using an S300 column equilibrated in STE essentially as described in Nehls *et al.*, 1993, TIG,*9*:336-337, and the products were recovered by centrifugation at 1,200 x g for 5 min. This step removes unincorporated nucleotides, oligonucleotides, and primer-dimers. The PCR products were subsequently applied to a 0.25 ml bed of Sephadex® G-50 (DNA Grade, Pharmacia Biotech AB) that was equilibrated in MilliQ H_2O, and recovered by centrifugation as described above. Purified PCR products were quantified by fluorescence using PicoGreen (Molecular Probes, Inc., Eugene, OR) as per the manufacturer's instructions.

Dye terminator cycle sequencing reactions with AmpliTaq® FS DNA polymerase (Perkin Elmer Applied Biosystems, Foster City, CA) were carried out using 7 pmoles of primer (Oligonucleotide BTK-3; 5' tccaagtcctggcatctcac 3', SEQ ID NO:8) and approximately 30-120 ng of 3' template. Unincorporated dye terminators were removed from the completed sequencing reactions using G-50 columns as described above. The reactions were dried under vacuum, resuspended in loading buffer, and electrophoresed through a 6% Long Ranger acrylamide gel (FMC BioProducts, Rockland, ME) on an ABI Prism® 377 with XL upgrade as per the manufacturer's instructions. The sequences of the amplicons, or GTSs, are described in SEQ ID NOS:9-503.

All publications and patents mentioned in the above specification are herein incorporated by reference. Various modifications and variations of the described method and

system of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the above-described modes for carrying out the invention which are obvious to those skilled in the field of molecular biology or related fields are intended to be within the scope of the following claims.

CLAIMS

WHAT IS CLAIMED IS:

1. An oligonucleotide comprising a contiguous stretch of at least about 15 nucleotides first disclosed in at least one of SEQ ID NOS:9-503.

2. An isolated cDNA polynucleotide derived from the genome of a human that is capable of hybridizing to a sequence first disclosed in at least one of SEQ ID NOS:9-503 under stringent conditions.

3. An isolated polynucleotide comprising a contiguous stretch of at least about 60 nucleotides first disclosed in at least one of SEQ ID NOS:9-503.

4. The isolated polynucleotide according to Claim 3, wherein said polynucleotide sequence comprises at least one of SEQ ID NOS:9-503.

5. An *in vitro* process for producing a polynucleotide comprising the steps of:

a) obtaining a polynucleotide template encoding a sequence capable of hybridizing to a GTS of SEQ ID NOS:9-503;

b) combining said template with a synthetic oligonucleotide sequence of about 14 to about 80 bases in length that comprises a contiguous sequence of at least about 12 nucleotides disclosed in one of SEQ ID NOS:9-503; and

c) processing the combined oligonucleotide and template preparation such that said oligonucleotide sequence hybridizes to said template in the presence of a DNA polymerase molecule and a sufficient concentration of dNTPs for said oligonucleotide sequence to prime DNA synthesis by said polymerase,

wherein a polynucleotide is produced that encodes at least about 50 contiguous nucleotides first disclosed in one of SEQ ID NOS:9-503.

6. The process of Claim 5 wherein said template is mammalian cDNA.

7. The process of Claim 5 wherein said template is mammalian genomic DNA.

8. The process according to Claim 6 wherein said templates are of human origin.

9. The process according to Claim 7 wherein said templates are of human origin.

ABSTRACT

Novel human polynucleotides are disclosed that correspond to human gene trapped sequences, or GTSs. The disclosed GTSs are useful for gene discovery and as markers for, *inter alia*, gene expression analysis, forensic analysis, and determining the genetic basis of human disease.

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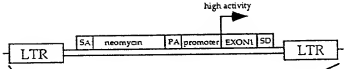
retroviral vector



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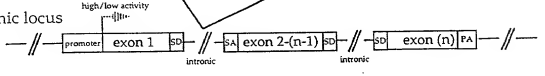

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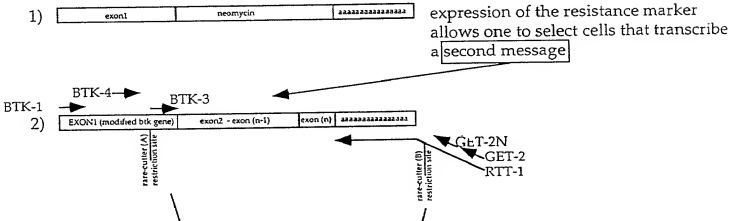

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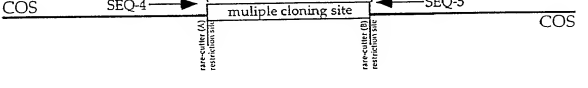
TST vector
(e.g. lambdaPhage)



DECLARATION
AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below at 201 et seq. underneath my name.

I believe I am the original, first and sole inventor if only one name is listed at 201 below, or an original, first and joint inventor if plural names are listed at 201 et seq. below, of the subject matter which is claimed and for which a patent is sought on the invention entitled

NOVEL HUMAN POLYNUCLEOTIDES AND THE POLYPEPTIDES ENCODED THEREBY

and for which a patent application:
☒ is attached hereto and includes amendment(s) filed on *(if applicable)*
☐ was filed in the United States on as Application No. *(for declaration not accompanying application)*
with amendment(s) filed on *(if applicable)*
☐ was filed as PCT international Application No. on and was amended under PCT Article 19 on *(if applicable)*

I hereby state that I have reviewed and understand the contents of the above identified application, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

EARLIEST FOREIGN APPLICATION(S), IF ANY, FILED PRIOR TO THE FILING DATE OF THE APPLICATION			
APPLICATION NUMBER	COUNTRY	DATE OF FILING (day, month, year)	PRIORITY CLAIMED
			YES ☐ NO ☐
			YES ☐ NO ☐

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

APPLICATION NUMBER	FILING DATE
60/104,292	October 14, 1998

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION SERIAL NO.	FILING DATE	STATUS		
		PATENTED	PENDING	ABANDONED

POWER OF ATTORNEY As a named inventor, I hereby appoint S. Leslie Misrock (Reg. No. 18872), Harry C. Jones, III (Reg. No 20280), Berj A. Terzian (Reg. No. 20060), Gerald J. Flintoft (Reg. No 20823), David Weild, III (Reg. No. 21094), Jonathan A. Marshall (Reg. No. 24614), Barry D. Rein (Reg. No. 22411), Stanton T. Lawrence, III (Reg. No. 25736), Charles E. McKenney (Reg. No. 22795), Philip T. Shannon (Reg. No. 24278), Francis E. Morris (Reg. No. 24615), Charles E. Miller (Reg. No. 24576), Gidon D. Stern (Reg. No. 27469), John J. Lauter, Jr. (Reg. No. 27814), Brian M. Poissant (Reg. No. 28462), Brian D. Coggio (Reg No. 27624), Rory J. Radding (Reg No. 28749), Stephen J. Harbulak (Reg. No. 29166), Donald J. Goodell (Reg. No. 19766), James N. Palik (Reg. No. 25510), Thomas E. Friebel (Reg. No. 29258), Laura A. Coruzzi (Reg. No. 30742), Jennifer Gordon (Reg. No. 30753), Jon R. Stark (Reg. No. 30111), Allan A. Fanucci (Reg. No. 30256), Geraldine F. Baldwin (Reg. No. 31232), Victor N. Balancia (Reg No. 31231), Samuel B. Abrams (Reg. No. 30605), Steven I. Wallach (Reg. No. 35402), Marcia H. Sundeen (Reg. No. 30895), Paul J. Zegger (Reg. No. 33821), Edmond R. Bannon (Reg. No. 32110), Bruce J. Barker (Reg. No. 33291), Adriane M. Antler (Reg. No. 32605), Thomas G. Rowan (Reg No. 34419), James G. Markey (Reg. No. 31636), Thomas D. Kohler (Reg. No. 32797), Scott D. Stimpson (Reg. No. 33607), Gary S. Williams (Reg. No. 31066), William S Galliani (Reg. No. 33885), Ann L. Gisolfi (Reg. No. 31956), Todd A. Wagner (Reg. No. 35399), Scott B. Familant (Reg. No. 35504), Warren S. Heit (Reg. No. 36828), Kelly D. Talcott (Reg. No. 39582), and Mark A. Farley (Reg. No. 33170) and, all of Pennie & Edmonds LLP, whose addresses are 1155 Avenue of the Americas, New York, New York 10036, 1667 K Street N.W., Washington, DC 20006 and 3300 Hillview Avenue, Palo Alto, CA 94304, and each of them, my attorneys, to prosecute this application, and to transact all business in the Patent and Trademark Office connected therewith.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF MICHAEL NEHLS (201)	SIGNATURE OF BRIAN ZAMBROWICZ (202)	SIGNATURE OF ARTHUR T SANDS (203)
DATE	DATE	DATE

SEQUENCE LISTING

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Zambrowicz, Brian
Sands, Arthur T.

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Encoded Thereby

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cctacttgta gttgcagaca aagaaacagg agatgaatta ccatgttcta ggactttgtg 420
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<210> 11
<211> 407
<212> DNA
<213> Homo sapiens

<400> 11
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gctgttctaa ccacgtaaga agcacaaggg tcaccggtta ctctccatga gaacaaaagg 180
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agatctgcag agcccagata agcatcccag ggttctggca gagggcccct ccagggacag 300
gaaggggaca ggaagccggc tttccgtgtc tgtaccgcct tccttgggaa ggataggaca 360
cctgtggcca tcaagtcatg atgccccatc tttctgaaac gaaaaca 407

<210> 12
<211> 200
<212> DNA

<213> Homo sapiens

<400> 12
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gcccagtccc ctctccacgc tataccctgt gccacctcca gacacttcag agaccaggaa 120
taaggccctc accagaagtg ccccctcaat cttggacttc ctatcctcca tggctgtaag 180
gaataaattc cttttctttc 200

<210> 13
<211> 128
<212> DNA
<213> Homo sapiens

<400> 13
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ggagccgtgc agttgttctc actggcagat cagtcctgtc cctccaataa aagagagggt 120
gatcttgg 128

<210> 14
<211> 142
<212> DNA
<213> Homo sapiens

<400> 14
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tgtactgctt ggaggagagc taccctggag catttgctcc agattctgca tgagcaaaaa 120
ataaactttt gctgcataaa gt 142

<210> 15
<211> 149
<212> DNA
<213> Homo sapiens

<400> 15
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acaagatgtg aacattcatc attatgaggc tgaatgtaaa atacttcatt ttataatgaa 120
gaaagtcagt aaaacaattt ccagcccag 149

<210> 16
<211> 166
<212> DNA
<213> Homo sapiens

<400> 16
gaagaagaan ctcnncctcnn catgagaccg ctgtggggat ctggcactgt ggttcctgna 60
tgcaaacant ggtctggncg tgcctgggcn gacaataccc ctttccgtgt cncgggaaan 120
gcccncctta aaaaaactga nggngttgaa aaaccagtaa accctc 166

<210> 17
<211> 113
<212> DNA
<213> Homo sapiens

<400> 17
accctgatna ngagaccagc tgaggcgaat tatgagtcaa ctaaaattat ccaaaagatc 60
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<210> 18
<211> 250
<212> DNA
<213> Homo sapiens

<400> 18
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acagccacca tgaccacctc atgcctccca tccacctgtt tcattaattt gtgcctggac 180
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ttcgactatc 250

<210> 19
<211> 387
<212> DNA
<213> Homo sapiens

<400> 19
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agtctagcca actcctcttc cagcgccttg ataaacaacc ccctcatgct gggaaccaca 120
gcagtgggct gtttttctcc ctcatgcacc ccaggaagcc tctcctcttt gcctgggctt 180
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tgagttttgt ttttagcagg aagaccttat tttcaaaaca aattgttaca cagaatttgc 360
cagtttacag aacagatgaa taaagac 387

<210> 20
<211> 216
<212> DNA
<213> Homo sapiens

<400> 20
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cctgtgccag gctcttgtgg atgccatcaa caaacccctc tgacacctct gacgggagca 120
tgtgaataac accgaataat cacaacaaat cctcctcatc ataaagcctt gcgnggactg 180
gcactcgcaa atatttaaat aantattaaa acactg 216

<210> 21
<211> 541
<212> DNA
<213> Homo sapiens

<400> 21
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gaaaactcta ctgatgacag gcaagaagcc agactgctca gacctagagc tataaggaaa 120
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tggctatgtt taagtttctc atagaaaaaa ataaaataac naaacncnaa aaaaaaaagg 480
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g 541

<210> 22
<211> 492
<212> DNA
<213> Homo sapiens

<400> 22
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ggcctcaccc agggcataca gctttcccag ctagcaaaca aacaagccct ggtcacagcg 180
gttatagctg gctcatggtc gctcacagac actctgggca tgcatttccg tgacttanaa 240
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gggccccatg gcccctccac accagcatgg tgctctgcaa aggccagctg ctcttcatcc 360
tgtctcaatg atacacagtt tttttcccca aaactttagt agcgccactc tccctatcac 420

tcgtctttta attttgcccc ttattgntcc ttanattaaa aaatatcctc ctttcatngg 480
agggttggac ct 492

<210> 23
<211> 273
<212> DNA
<213> Homo sapiens

<400> 23
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gagagctgtt tgggaggctg ggaaggtcca ttagaagcat aattctattc cagaggtggc 120
ttggcagatg gagcatatca tgggttaatt tctcagcatg tcacagaaag caattcctac 180
tagacctgaa gaaagtggct tctctcttaa cagaatgtta tctttttcta gagagtaata 240
tgtttttatt aaataaaaag catctaatag tac 273

<210> 24
<211> 495
<212> DNA
<213> Homo sapiens

<400> 24
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gagaaggtta tgtctcctga gttctagttc tccgtcctga agtccatgta atgtgagtta 180
caagccgtct gcagaggtga gcattcgact ctggccagct caagttattc ggcaaggtgt 240
gattgtccag tcttgaggct gtttgctggg agaagcacga cataggctat tgccagtgcc 300
aaggagaaca atcctaataa gactgacagc cctgcccaaa tgacatggca ttgaaaatga 360
cacctgactg aatgaanctg acccttgagg taggcacttg ancttnttca aaaaanaagg 420
gagggaccag ccncaganga ggcatggatc caaacttttg ggatcctcan aaatgtgtga 480
agtgactcct tcttt 495

<210> 25
<211> 468
<212> DNA
<213> Homo sapiens

<400> 25
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tgctgtactt ctgtgtatga ataaattaat gttctgtttg aaacatcagt ctaagggaga 120
agagaatgta catgcagata gcctttctat cgacctctat aaccaagacg gcaagcttta 180
tgaaggagga gatgctgtct catttacaag agccaaaagc agtgttccct aactctttggc 240
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ttcatttgtg ttttctcgga gtaaatttta gtgccgtgat accatttggg tattcattaa 360
tatttatcac acnaaggaat taaatgggtc tcccgaacct ggcnttaacc tccttgctaa 420
cctaatattc attcaacaaa tattaactgg gcatcttcaa tggggcag 468

<210> 26
<211> 176
<212> DNA
<213> Homo sapiens

<400> 26
gatcatgaat ggaatgacac actctgaacc gaagagacct tacagatcat ctagttctcc 60
agccttgaag atggggaaac tgaggctcaa ggaaggcatg taaacagcaa cctcgggatt 120
ccatttaaat tctgcctctc tggatctgct tcctgatata taaaatggta ataacc 176

<210> 27
<211> 104
<212> DNA
<213> Homo sapiens

<400> 27

actggcatga aatgacagat atacagagga cccttgaaca acctgggttt gaactcctca 60
acatggacac ttatacacgg atttttctca ataaaagtga cacc 104

<210> 28
<211> 472
<212> DNA
<213> Homo sapiens

<400> 28
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gtgggtttgn ggaacttggc agcccntttt ttttaccaac taaataaaaa aatctggtat 120
tncaaaaaca tggaccttna ttgnggccnc ccnttttnct tnattaaaaa aaccaaaagg 180
ggggccnttg gaccttaaag gnactaaaat ggncaaggggg gtggggacca anaaatccaa 240
agtttgnccn ngtccccacc aggttttttg nttttaaaa taaaccccaa atttgggnca 300
aaaaaatctt tccttcaaaa agaccaaaaa ancncgattg aaaggggggа aaaaatggcc 360
ccntttggg gtttaaaaat tttaaaaacc aggnaggacc tnccccttt gngtcctttt 420
ttcaaggggt tcaaaataaa ataaaaaccn atttccttag tggattttaa gg 472

<210> 29
<211> 443
<212> DNA
<213> Homo sapiens

<400> 29
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tttcaatggt tctgttgaac atgcaattct cactgaaagc accagatttc cgcgtaggag 120
ggactcgggg gcaacgatgc aattggaaga actgcaccga aaatgacgat gtcttctcat 180
gcatatgaat tatccaaagt gtgggaagat gcgcccccac tggagtacgc tgaagccttt 240
aacccaagta catttaatgc tgcgaagccc cgagtgaggc aaaggtgtct ttttatttta 300
gaagacattt aggacagttc atgtcactct gcacagatgc actgaaattg attgnggggg 360
caaactntaa agagagctta tgctccccaa atctgtttcc gagccaggta ggatgatgaa 420
ttctgaggtg ggactggagg ggt 443

<210> 30
<211> 254
<212> DNA
<213> Homo sapiens

<400> 30
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gtgggtagaa gatcctgaag ttggtccttg ctccttttca gaccccaacg ntctcagtct 120
ccctctttcc tggctagtgc attacaggca cactaaatat tgttggtggt gatgatgaca 180
gaaattacct tttcctaata tttcctatag gtaattatta gaaaattaaa agtagccact 240
tgcaaattaa aaag 254

<210> 31
<211> 120
<212> DNA
<213> Homo sapiens

<400> 31
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ctttcccact ttagttttca tcttccataa tttacgaata aatgcataaa atggaaatgg 120

<210> 32
<211> 124
<212> DNA
<213> Homo sapiens

<400> 32
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cttcgaattg tattgtacat ttgcattgat gtggttattt tcatctaaat aaagtcaaac 120

aggt 124

<210> 33
<211> 373
<212> DNA
<213> Homo sapiens

<400> 33
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cttgccctgc ttgcctaaca aagacctcct gggaggagga cccagaagag ggcagggctg 120
aagaagagtc acagctgaag aatgtgactg tttgccagga aagccacttt ctttctgcag 180
caggattaga attcctacaa ctccagccaa aggaactggg ttgggaagcg atactgcaag 240
cattcatgtg cttccatcct ggtcttcagc ttagccacgg tcctgcgggg acagtgagtc 300
cctctctgag tggccaggac ctncacctgg cccacaggaa gcctttacca gcaggaagcg 360
aaacgggatg ggg 373

<210> 34
<211> 480
<212> DNA
<213> Homo sapiens

<400> 34
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ggaagcccct ccaacaggca acatgactgc agcacaatca actatggctt tgctgatctc 120
gtgtatcatc atcctcatca tcctcatccc cgcaattgca gcaaacgtcc agttgtgcac 180
ttgctgctga tgatgaataa atgtatagaa caggaaaaaa tgtatctcac cttcagacag 240
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gtggtgcagc taagtgaaag cctgctgact tgtagacata tgagtaaggc catgcttgat 360
cacctggctg ccagctggcc tgccaactaa ttggaggnac ttggaaagan tcnacnaaan 420
atcacccccc caggtcaaat aaaccccagc cccctccntg agaatgatga actaaataat 480

<210> 35
<211> 100
<212> DNA
<213> Homo sapiens

<400> 35
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acaacgacta tccagatttt tcttccaact ttactttaag 100

<210> 36
<211> 183
<212> DNA
<213> Homo sapiens

<400> 36
gcagcaacca cggtcgtaat gggatctgtg actgtcacca gaagaaatca ccaacagttt 60
cgtatcacgt gagagttttg caggtgcctc caaatgccgt ccatgctcat caacactgtg 120
acatcagctg cggttcttta atgcatgtga taaggaagca cgtatattag aagtttgggt 180
ttt 183

<210> 37
<211> 144
<212> DNA
<213> Homo sapiens

<400> 37
aaaggacttg tacctcccag aagttcacgg aagtgctcag gacaacagaa tattgtgagg 60
ccaacacagc aaacagagca acgatgagca gccacttttg actttggttt ccttattcag 120
gaaataaaac agatgatctg acag 144

<210> 38

<211> 140
<212> DNA
<213> Homo sapiens

<400> 38
gatctgtaga gagacagcgg aggcaaagat acctggagcc gatcanagaa gagatgccca 60
ctctgaaatg gacacgccta aggagacatc aaaatcttca ccaaaccctg tctaataata 120
cagttaaatc aatatcagag 140

<210> 39
<211> 442
<212> DNA
<213> Homo sapiens

<400> 39
gagagaatct aatatactca ttcacactga ggtgtaaggc tctaagaaga tgtacactgc 60
ctgcccaggg atatatccag ttcacctgga agctaagcaa gaagaattaa aatacagaaa 120
tgggaataaa gtttgcaacc tctccaaccc tttgttccag gctgcttttt acgcctcaaa 180
acttaccaga ttttgtctgc acctcccaga caacctcaga aatgtgtttc ccaaaaatct 240
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agatgggaaa agttgggaaa ca 442

<210> 40
<211> 414
<212> DNA
<213> Homo sapiens

<400> 40
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aaatccatga tggcagctta ctcgatcttt gaagaacctc tagcttcatt atactccaac 120
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taaagatacc ttgtgtctgt aacttcctga ttctcaggag ctgacatgtt gatgtgtgag 360
ccacactccc acttctcatg tcatgaccat cgaataaaaa ctggtcttgg tttt 414

<210> 41
<211> 271
<212> DNA
<213> Homo sapiens

<400> 41
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ggagattttc agaaaagcca tggccttacc agtgaaggtt acacagaggc cactggagtc 180
aagtaattca ttgctcctta ttacatttag gcacttcttt atccatcatg caggctattg 240
ggattaaaat gggtccttttc aacaatgagt c 271

<210> 42
<211> 111
<212> DNA
<213> Homo sapiens

<400> 42
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atgaagagt ccccctgca gtaccacaat aaaaatgtag tgtgaatgag g 111

<210> 43
<211> 473
<212> DNA

<213> Homo sapiens

<400> 43
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agaagccaag cagaacatgc tagcctgtcg attttgtctt ccattaaggc ttcagcagaa 180
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tattgtaaaa atgaataact ataggctata gactggatnn gggaanccta atccctaatn 420
gngatggaat tgggaggngg ggctttggga tgccattatt taataggtca aga 473

<210> 44
<211> 429
<212> DNA
<213> Homo sapiens

<400> 44
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tacagaaacc tgagcgggtc anaacgttca tcttcatcta gccaaggtga aagcacccag 120
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gctttcttca aacaaagtaa atgaaaattt cagtggctcc agcagtcggg actgttaggc 360
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taaaaatcc 429

<210> 45
<211> 489
<212> DNA
<213> Homo sapiens

<400> 45
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ttctcagaaa tggctcacaa agaaacacaa aaaaaggntg tctgaangna aaancnagaa 180
aaggttccct tcnnnaaaan gnaaatggan cnttnancnt ttttnngggnn gcagaagtgc 240
cacggncntn tnantgcggg taattnaaan agggncanaa cactttcttc aggccacccn 300
agggangttt tatattnccc atataaagan acaaattccc acantgtgcc ttccttgngg 360
tntntccaac tctttgccaa caagaggcca acccggggng ggccccccncc aggggaaaaa 420
aacctttgg ggnggancc cctttgggca ntgccaangn ccttttgaca tttcaccggc 480
gggaagaga 489

<210> 46
<211> 358
<212> DNA
<213> Homo sapiens

<400> 46
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acgtcttcca ggcaccagga agaaatacga ccaacctccg taacaaatga gagaaacttc 120
acctgactgt gttttgtgca tttggnttat gagncgtttt aaaaacgtgt acttttactg 180
ctgcgttcag gttttcagcc atagaatatt ctagaaaaaa atagtgataa catttatttc 240
accgctataa ccctgaatgt gtagctgtgt tttttaaaaa aacatttttt tacaattgta 300
gaatatgtaa catgcctcca gaaacgtgcc ctaaacacaa atatatatt tggcaaat 358

<210> 47
<211> 177
<212> DNA
<213> Homo sapiens

<400> 47

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gccaaggcag gtggatcgct tgagcccagg aattcaagac aggcctgggc aacacagcaa 120
gaccttgtct ctataaaaaa ataaaaaata aaaataaaaa taaaaaaaag atcagtc 177

<210> 48
<211> 536
<212> DNA
<213> Homo sapiens

<400> 48
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ccccttggc ccaaggatga gtacccacag cagcaagctc ttccattgga aaccacgctg 120
aggaagacat ggtcaagctc tggcagcaga tcaagctgtt atggcaagaa ttcctggttc 180
tgcgtcccca gcatgtaata tagaagatct gggagtgggg tcttgggtct gtaatgtctg 240
tgatatggct cctcacatct tcttgtgtag agtgtcatgg ccaaaacagg aataaccgtg 300
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agccaagatc tgntactaaa attaaatncn caatttaatt tccacaagct acatacctcc 480
cttcanaggc ctgccaaaat tnttaatgga ggacaatgaa agttcgtaac cttctt 536

<210> 49
<211> 374
<212> DNA
<213> Homo sapiens

<400> 49
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gaatgcatgg gcaaatgatc tctggagact ctagcaatca ttccgaagtc tgtgttcaag 300
cagtaaacaa acagcacact cagtaaccag tattcttgta aagatggagg atggtaatta 360
cattctgtga ctag 374

<210> 50
<211> 595
<212> DNA
<213> Homo sapiens

<400> 50
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gcagtagaaa tgaggccatg tgactctcca cgctggagga ggacaggcac tgaggctcc 180
gccagctcgc tcttgcttgt gtgatgcctg ccctggaac ccagccaccg taccgtgagg 240
aagccaagca gccacgtgga aaggccatta caggtgttcc agccacagtt ctcatggagg 300
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agagagaatt gagtattatt gctgaactct gcccaaagtg cagtttgtat gcaaaatact 480
tcttccctta ttttaaagtg ataacttttt ggagagactt ttttacacaa caagtagata 540
atggaacaaa tactacttat gatttttgca gagtaaatcg gcttctcgct tttcc 595

<210> 51
<211> 268
<212> DNA
<213> Homo sapiens

<400> 51
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ggagtctgca ttaaaaacac tactctgggt agagataaag aaagggactc tctgagatga 120
gggaaaagca gtggtttcta atctgtggtc cagagatctc tgtcgggatg aagaatatgg 180
agggagaaac aagagttatt gtaaagggtc tacaaagctc tacgtatgca aagcactatc 240
tatagactga ataaataagt cttgcact 268

<210> 52
<211> 60
<212> DNA
<213> Homo sapiens

<400> 52
atatttcgct ctgaagaaac atcattagaa ataaataaat aaaattaaca tataatacct 60

<210> 53
<211> 419
<212> DNA
<213> Homo sapiens

<400> 53
tctcaatacc ttcacagagg tgaagaagca gcaaccaaat gaattagaca gcaacatgat 60
tcctagagaa tggcaagacc aattcttcaa ctacttcttc agcatttctg aaacatatgg 120
aagatggccc attgtgctct cttaattctt tgataatctg gacattgact tttccattat 180
atgacctggg cttgtgggca tcatgtcata atgcacctgt tcagacatct ccctgtacca 240
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ttccattttt gnttacagng cctaaaatta tttgagcagg ttttcacctc ttctctgaat 360
aaacacctta ttagtcctta aaangaaang aaaaagggaa aataaaactt ttaaatgca 419

<210> 54
<211> 450
<212> DNA
<213> Homo sapiens

<400> 54
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ctctgtgatg aagaggccac ttccatttaa aggcagcgac acttagaaaa tcacaggcat 120
taaaacttag aagaggtcac cttatccaac gtcccagcca gcacagccat cctttcacag 180
catccatgac attcagcctc ctctcagaca tgggaagatc acctcttcat gaaacagcag 240
attcttcaag gataaggaaa tggaggaaca aagcagtgaa gtaatctgtc caaagcccaa 300
aagttgaatt gttgaaactg acatctgaaa gcaagtagcc tggcttcaga gtatatgctt 360
ttaatcgctg tgttatatac tgcctcttta tatgtgataa tatagtatat ttattaagtt 420
attaaaagaa acataagttt ctttgttgtc 450

<210> 55
<211> 172
<212> DNA
<213> Homo sapiens

<400> 55
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tgcctctgac attttcaagc ctaaagatca agagccatca tcttttacaa gagttgcagt 120
ttggtcttaa cctccaaaaa agaaacttct aataaatact atttccttct gt 172

<210> 56
<211> 211
<212> DNA
<213> Homo sapiens

<400> 56
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gaaaaagaaa aaaggagaaa tcaaagaaag agaaagcaaa aagagcatat ttggatgtgg 120
aagaagaaaa agacaagttg aactgtctta aattccagcc catgaaagcc ttccttttttt 180
taaataaagt ttttgttttg ttttggtctg g 211

<210> 57
<211> 328
<212> DNA
<213> Homo sapiens

<400> 57
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aatttcaaat ttccagcctc cagaactgct ccaagaaatg gaattttatt aaaagatgga 120
agaggaggat atttgagaga aggggaacta cctaatactg aaaactaata cagtccagga 180
tacatagaag atgatcaata acacttattc aatctaaatt accctatcag caagtggaga 240
gttctctctc gggagtgctg ttttctttcc tgccagtcag ctctgtcagg ttgaatagaa 300
agcgataaat aaagaggaaa agaattcc 328

<210> 58
<211> 208
<212> DNA
<213> Homo sapiens

<400> 58
gagttggttg ttaaaaagag cctggaatct ccccgtctct ctctggcttc ctctctcact 60
catgtgatat ctgcacttgg aggctcctct tctctttctg ccatgaatga aagcagcttg 120
agaccctcac cagatacaga tgctggtgcc atgctctctg tacagcctgt agaccatgag 180
ccaaataaac ctgttttctt cacaaatt 208

<210> 59
<211> 334
<212> DNA
<213> Homo sapiens

<400> 59
catatctcaa aaatcaagat gaanccttaa gctttctacc cagatgttgt gggaacttga 60
agacaaagtc tcaaagagac tccgttttgg tcaacaatta gcccttccac atttggatcc 120
tgggccacat gtggaaataa agagttccag aagaattctc ccatgaaggc attggaatgc 180
ttcaatacat agttttgtgc caaatctaca ataatcttcc caaaagaaag actcttcagt 240
gttctggatt tttcgggact tntcttattt tcttgtgcaa catcttaaca caaactagaa 300
taaagatgac atataatcat ctgcattcat gaat 334

<210> 60
<211> 177
<212> DNA
<213> Homo sapiens

<400> 60
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ccagtccctg caaccactga tctgcctcct ccctctatgg cgtcacctgt ttggaacatt 120
tcatgtaaat ggaaccatac aagatgtgac cttttgtgac tggcttctct cacttgg 177

<210> 61
<211> 381
<212> DNA
<213> Homo sapiens

<400> 61
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tgtgcataag ggaagatgag aggctggttg acgcccaccc ttcaccagtt ttgtaaataa 120
caagctggcg cccagaacc catccacagc agctttttca gtggcattat gcattcgtgg 180
tgcaagcatc cttactgtgc ttcaatcagt ggcttcagtc gtggccggcg cacactgatg 240
gagtttcttc ctcgtcgcgg gtcatatttt cctctttgca tgtctgatga cttttgatta 300
gatgcaggcg ttgttcactt tccctgttga gttctgagta tatttgcatt cctattaaat 360
atccctgngt tttgctctgg g 381

<210> 62
<211> 141
<212> DNA
<213> Homo sapiens

<400> 62

gaaataaggg accctggcat ggatggagca tgtgaaacta tcaagaacag tgaaatgttt 60
cagatttttg ctatttgcca gtttcgtttc atgaatgctg gcagaagacg cctgaatcaa 120
agataaaggc tgtttttact c 141

<210> 63
<211> 581
<212> DNA
<213> Homo sapiens

<400> 63
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gacaggagag ctcagggtcg aagtcggccc ggccgcctgg agctccaagg ggacaaatgg 120
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ttgcccaact caatggctca agaacctgcc ctgtcctgct tcgggcccag cattccatcc 240
tctgaaagaa cacgagcgtc cccacatgct ccgtagggac catcctgcct ctgccctccc 300
cacttcacca gaagaactcc tcctcatcct tctgggccaa cttggcagca actcctccgg 360
gaagccttcc ttgctctccc aagacacgga caggcacccc tcgtacgtgc caatagcatt 420
cccatcagca gttgtcacac acacaaggct catgacctcc ctccccacct gtgcccccag 480
gggaggggct tncttggggg cagggccatt tcgtcgtcat cttccagcac cacacacact 540
cggtttgctg aatgcttnct aaataaattc ctgccaaatg c 581

<210> 64
<211> 244
<212> DNA
<213> Homo sapiens

<400> 64
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tgttgctgag aacacttgtt cccacttctc tagcaggcaa ggatctgggc aggacaacaa 120
ccacaggcat gtgctttctc atcatgtgat gtcatctgcc aggtcatgat gcagcaagaa 180
ggccctcacc agatgccacc cctccagaac catgagccaa ataaatgtct gttctttata 240
aatg 244

<210> 65
<211> 362
<212> DNA
<213> Homo sapiens

<400> 65
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gcctgtggcc ttccagctat tcagtcaaca gcatatgaaa atgcagttca ttaaaagtaa 120
accatccaag tcacctgttc actgtggctt cctgtcagga gggacagttt agatgacttc 180
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tgctatctgc aatagtgaca tctggtggct tctaagttct actgcacctc cttaaggcag 300
gaaagcaagc ctggctttta agcagtattt gtgaaaaaat aaaggaatta catgagttct 360
gg 362

<210> 66
<211> 418
<212> DNA
<213> Homo sapiens

<400> 66
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ccagagaggg atgatgcagg ctcttccaga acctgtgtcc tatgcctcaa gccttctttc 120
cctcctgctc gctgacaact gctgaagcag aaactaagat tacgacacta ggtggcagca 180
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tttggagagg ctccacgaaa aagaccagcc cccaaataac agggagactc tgcaatgctt 300
ggtttccagt gatgatcaac actttaaggg ccaatggaat tcacccttac aggggaaagg 360
ggaccgttga antancctgg ggnggggagg ggcatgctcg agaaacccta cctaatgc 418

<210> 67

<211> 322
<212> DNA
<213> Homo sapiens

<400> 67
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tcaaaagatg agtaaaggaa agtctgctat tttcagagtc cacttgtcct gagctggttt 120
tcttctaaac cacatcacaa aagagcacga tgctgtgaac ctctcctttg gactcaagtg 180
tactaatggg gaggaatggc aagttacatg cattatttct ggattctata aaaatgaaag 240
tgatgggaat taaaaataag ttcattaata ttgtaattta tagttctgaa gagctttagc 300
aaataaacta aacattccaa at 322

<210> 68
<211> 317
<212> DNA
<213> Homo sapiens

<400> 68
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ggtggggcgc atgcccgcca ctggactgaa agctgagtca caggaatcgt acccctgcag 120
cgggccaggc cctccaggga gggacaccgc gcccttgtgt ggagatgtcc acagtagaca 180
aaggcagttt cgaaataaaa gaatgcctgt caccccaggt gccaccccga cccttagtta 240
ttatgcactg gtccccaaga gcaatttctg cgctgctgtt gcaaaaattc atcgtaatga 300
aataaacgta aaagggg 317

<210> 69
<211> 678
<212> DNA
<213> Homo sapiens

<400> 69
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ggaggcacaa aagtcccatg ccgagagaga agtcggtaac tacgcctgtg accgggagag 120
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gacactttga agtgacaccg ggacccaagg gttctcaagt tcattatttg tgaagaaatg 480
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tttggaggnc tttcctggat caacagatgg aggacttttc aaaagcagac gaaagtgaat 600
gggatcactc acacctctgc ttcggacaca gngaagccca gatggagaag aaagaaaact 660
tggncaaagc tatacttg 678

<210> 70
<211> 257
<212> DNA
<213> Homo sapiens

<400> 70
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atcccagagg agaagccatc tgagatcggg aggaggagaa atggaacatc aggcggagga 120
aacagcccag acaatcgcac tgggacgtga aaacccttgg gctgcatgcg gggagaaaac 180
cagaattggg gatggttagg gttttggagg gaaacacagg gacatgtgac caaaaataat 240
aataactact gttactt 257

<210> 71
<211> 491
<212> DNA
<213> Homo sapiens

<400> 71

gtaacctaat gggttttcta gccaagccgc aagcatgtaa ctgcaacttg aaggaggaag 60
atgtctttag agacttagaa aagaccagca agcttcttta caaaatggtc tcttcaatcc 120
tggcatccac ttgggaccaa tgagatggga tgttcatcct catagatttt cacatatgta 180
tctttaatgg tatccccagg agcctctgaa gtgcatcagg actttatttc aatgaagttc 240
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cctacttatc agattggcaa aaannaaacc aggtcataaa acccctttg gtaaatatat 420
ggaaaaaaca catcttttta tatgcattgn catatataca tacatatata tgctgcatta 480
atatatatac t 491

<210> 72
<211> 196
<212> DNA
<213> Homo sapiens

<400> 72
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ttgcacccag acacggcatc tcagacactg cacaaattaa gaagtcaccc tcaaaacctc 120
tatacagtgc aggaatacag ctaagacacc acacccgagt actaacatct gcaaattctg 180
aaaagctcct cataat 196

<210> 73
<211> 511
<212> DNA
<213> Homo sapiens

<400> 73
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aacaagtcag tctcaaacat aacaacagac actggggagc tctccaacaa aagatcacct 120
cccaaagaac aggatggtgt cgaagactga atgccagcct gaggaaacag aaatactaca 180
gaagcacgcc agagcctgca gtgtctcctc gctgcctctc aatgaactgc taaaagacca 240
agaactctgc tgagagataa gaagagggga gggtgtgctg caggtggtgc tgggaggccc 300
agaccttctc ctgacatctg gggctggcta caggaaacag aaacatcacc caggccttgg 360
cgccgagaca ggacagaagc agattgtgac tnaaatcttc nggnnggaaa ggggggcctt 420
tcnttttntc cttaggggnt anaacnaaag cccanaaggg ttcatccaaa ggnaaccctt 480
aaggcagttt natgatccct ttcaaccttt t 511

<210> 74
<211> 499
<212> DNA
<213> Homo sapiens

<400> 74
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ccggcctcat ggccttggg ggttgtcgtg tggaatggag atgacacgag tgctgcatgt 120
gaggtcagtc aggatctttg atttggagc acaagccttc tgcgtgctac tgactgggtc 180
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acccagatct gcgttctcca cctgntgnca catgaagcng gggnggtnaa aacagaccng 420
ggaantggnt acctcattac aatgccccnc tgactggtnt aanttcccna naggggttat 480
tggccatttt gttcaatga 499

<210> 75
<211> 427
<212> DNA
<213> Homo sapiens

<400> 75
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ccagtcttat ctccgtcctt atcaccacct taccatgtca tcctggcgaa gatgccatca 120
caggagtcag ggttgaagtc caggtttaag gtgcatctag atgggttccc aggacgcctg 180

aagtagcctc aagaggccca aaagaaaaag ctcctctggc acagtctcct aatggtgaca 240
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attatttccc actgaaattc aaacctaatt catttatttt ttattctcta taaaaatgaa 360
aaacatcact gnggcaagta acttgctcaa tttctnacaa aaaaataaan aaaaggtggt 420
tggattc 427

<210> 76
<211> 286
<212> DNA
<213> Homo sapiens

<400> 76
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tcaccatgca ncttatgcaa aatagttgtc aagctggaag gatgcaagcc caatctttgc 120
caccacaaag gaagataata aaacccatac gggagaaaac agagccacag atggagacag 180
tcacattcct ggtgacagtg tttgagcacc tggatccagc ccaacctgag gccattttct 240
cctaggcttt ttagatctgt gaaccaataa atccccgctt taggag 286

<210> 77
<211> 279
<212> DNA
<213> Homo sapiens

<400> 77
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aggaagtgat ggttgaacac gatgggacta ataagaagga aacgtagtta gagtgatctt 180
attcatttaa aaacaaaagc agcaacaata cagcagtcga ggaaaagaat caattctatt 240
taagcaaagc aatttaaagt aataaaaaat gtttccagc 279

<210> 78
<211> 481
<212> DNA
<213> Homo sapiens

<400> 78
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attggcatca tgtctccaac attctgaagc caaggctgag gatatacaag gtctggaatc 180
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ataagtattg gctggggtga ccattccatt tnctggnccg cccaaggana ttttgnaang 420
taacanaaaa gggccatnat attttccttc tctaacctgc cttgggancaa gccctaaaat 480
g 481

<210> 79
<211> 200
<212> DNA
<213> Homo sapiens

<400> 79
agagctcaca gcatcctgtc tcctccagaa gctcttcccc agctgaaatg gaagtgaaag 60
actggtagtc tcctcctcaa ccacccacct cctggggccc tgactgtgtg gatgaactcc 120
tcacacccag gatttgtgtc tccagtgaaa agcagcaatt tatcctacac tgaaaatttc 180
ctgaataaaa acagttcacg 200

<210> 80
<211> 239
<212> DNA
<213> Homo sapiens

<400> 80
caggagcatg caacacctct tggactcgat gaaagctgtc gccacaggtt tcaaccagtc 60
agtactctga aagagcatct tgggggaaaa aaaagcgtgt cagacattca tcttcataac 120
cagaaagtga agtctcgcaa aggaaaaaga caagactaaa gggaataaac catcgttgtg 180
tgggcttttt cttccactca gcatctcttc ccttattaaa atgagaggga taacttaag 239

<210> 81
<211> 495
<212> DNA
<213> Homo sapiens

<400> 81
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gaaagtttca caagcacact ttgttcagtt ctgcagctta ccaggaacac tagaaagcac 180
tccagcactg tgcctggggg ccatttgaaa cagcaaaatc atcaacaaaa accacaaaaa 240
tgcaaaaacc atggcactaa atagaccatg aaaaggacac ctgtttactg catgacctga 300
aacaagaagg cggagcgttg ccttgttcga cttcagctgg gaagataggc gtcaggggac 360
tcaaactttt cagcactctg ttatatctgn gaatgatcac aaaaaaactg gggagtntta 420
tttttggggg ttacnaataa attttacca agtaagcttg nttcacaaat acanaattnt 480
ggggataatg aaaat 495

<210> 82
<211> 98
<212> DNA
<213> Homo sapiens

<400> 82
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aaaaccagga aaagatggct catggaagca aagaaaac 98

<210> 83
<211> 486
<212> DNA
<213> Homo sapiens

<400> 83
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gaggaagagt ctgagctgca tatgtcaaga aggagaaagg ggaaagaagc aaggagcgag 120
accagaggga gccacgcaga aacctctggc ctctctgcac gtctgtctta tcctacagag 180
tggcgactct aaaaggccaa gggtgccagc gcccagcgac agttccacagc ctgagacacg 240
ctttgctcac acgcctccct cctcctctgg ctcctacctg ataaaaagca ttaccggttt 300
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agacatcata agcagggaga aggaacaaaa ggcanantgt gtncttaagg agggaggcan 420
tttgcaaaag cnccactntt ttcaccttgt ccacagaata aagggttgaa gactaaaaaa 480
aaaatt 486

<210> 84
<211> 280
<212> DNA
<213> Homo sapiens

<400> 84
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cacncantcg agtgtggagg ccccgaggaa gatcanctnt naanacacag gcaggcaaag 120
ggcagacctc taaggagatg gangangaat gacanagggc nngaagaatc ntgtgaggga 180
ctgncanana agccagtgac naaaacttnc agaagagctg ncaacagtac caaacaaagc 240
agaagagtct caaaagatta aaaataaaat ttgcttccat 280

<210> 85
<211> 408
<212> DNA

<213> Homo sapiens

<400> 85
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gaaccagagc tccttgcctc cctcccagcc ccccacccaa gtaacacgtt cctgatcctg 120
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<210> 86
<211> 477
<212> DNA
<213> Homo sapiens

<400> 86
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ttgtgccctt gaaaactgaa cagaaaacaa ctggattgna ttttttcttt caccaggaaa 420
aaagacaatt ttttnttttgt tganaangtc ataaaggcat tttacccact tattttt 477

<210> 87
<211> 500
<212> DNA
<213> Homo sapiens

<400> 87
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ccaaatagaa caaaaaggct 500

<210> 88
<211> 381
<212> DNA
<213> Homo sapiens

<400> 88
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gacatatcct tgcaaaaaaa tgttcagctt aagcctctan actaacttct ggtttacaag 180
aanaaaaaag aggggcccat ttccaaaaag actcctgcct tgaactcttc aaaatgccna 240
tgncacaggg ggaaaaaaga tgggggaact ctactacntt aaagctaaag aaaaatttna 300
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cttgntnaaa agggggggga c 381

<210> 89
<211> 458
<212> DNA
<213> Homo sapiens

<400> 89

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agatactgcc acctgctcca agtgtcaaat ccagaagaca aatggcctcc aatggtcttt 360
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tttataaaat aaaaactgca tgaattatca aaaaaaaa 458

<210> 90
<211> 227
<212> DNA
<213> Homo sapiens

<400> 90
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aacctaatca gcagtctgaa gtcaagccca gtggattcca gccaagcaca gcagaaccac 180
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<210> 91
<211> 256
<212> DNA
<213> Homo sapiens

<400> 91
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gcaaatctat aaaacatttt gaacttgtgg cctataaacc accaaacatc atgcaggtca 180
ctgatgtgag gatctgctgg gcttatggca tttgtgacaa acccaatgat tcttttatta 240
caacagctta taaatg 256

<210> 92
<211> 305
<212> DNA
<213> Homo sapiens

<400> 92
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ggcct 305

<210> 93
<211> 190
<212> DNA
<213> Homo sapiens

<400> 93
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agcaatggct gagtctacgc cctgtcgtcc cctcctgggt ctcacagaat ggaaataaat 180
gtctcaactc 190

<210> 94
<211> 509
<212> DNA
<213> Homo sapiens

<400> 94

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gttccctntt ccttttcnta agccaagcac ccttatgcca ccatcatntn tnacttanac 480
cacaacttta tcctnctgac atgtttacc 509

<210> 95
<211> 419
<212> DNA
<213> Homo sapiens

<400> 95
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aagggaatgt gtaccaggat acacataata aagtcccctg gccaaagctg ggattcctcc 360
tggccaagcc agaggagtga ttcaacttaa gagaaaattg gaaggaggac atgtggaat 419

<210> 96
<211> 95
<212> DNA
<213> Homo sapiens

<400> 96
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ttgacctggg gctcagacat ctcagactct tgtag 95

<210> 97
<211> 505
<212> DNA
<213> Homo sapiens

<400> 97
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aaggaaatgc nccaaaatgt taactgnggt tgacactgaa gggggaattn gggctttgtc 480
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<210> 98
<211> 500
<212> DNA
<213> Homo sapiens

<400> 98
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cacgaacagc ctgaccctgc tttcaaccag gaagttcaag ggaggcagga ctttacggtc 180
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cacccaaatc gaagaggata tcgtttcgca tcagggacac tcgtctccac acctcctacc 300
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agaaanagga aagacccggg ctgaggcacc aggaagaagg gacgcacaag aacctatcat 480
tggagcttgt tcgaggccag 500

<210> 99
<211> 482
<212> DNA
<213> Homo sapiens

<400> 99
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gtggagcacc agggtggaga gagtggaata agcagcaaaa cgaaaaattg gatgctgttt 120
tcaaaagttt tgttctcatt cttggattat agattatcta aagggaaaat ttaactcaac 180
caaaaaattc gttcagctcc atgaagctaa agatgctata aactgactct ttcctaaaga 240
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agggggggaa atctgaaact gtcagcccca aggnggaaca aaatgaaang gagaaaaaaa 480
at 482

<210> 100
<211> 508
<212> DNA
<213> Homo sapiens

<400> 100
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accacctttt gtcacccttg agacttataa ccaggccagg cgcgatggct catgcctata 480
atctcagcac gatgggaggc cgaggcaa 508

<210> 101
<211> 376
<212> DNA
<213> Homo sapiens

<400> 101
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aagacctgta gttctgcaac acagatgctc atcagaaaaa tgtgggtaac cttttcaata 360
ataaaaccct ggaccc 376

<210> 102
<211> 304
<212> DNA
<213> Homo sapiens

<400> 102
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gttgcaggat catacgtggg aagtggaggg gttcccatgt gaccttctat gaagatcaga 120
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ctttggaatg ccagaggatg agatccgtct tgtttactaa gagttgtnac ggntcccctc 240
accttacctc ccaaatcctg gtnaggaacc aggacctgcc aaggtgaagc actgatacat 300
tttg 304

<210> 103
<211> 501
<212> DNA
<213> Homo sapiens

<400> 103
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tgccntnccg gccggtgcca a 501

<210> 104
<211> 431
<212> DNA
<213> Homo sapiens

<400> 104
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ancananagg ggctcangac gctgtgagac ttttccattt cctttgcctc ccagcaggcc 120
gngaaagagt cacttttcct tgaggaagaa agaaggctct gtgtgcaggg caagggtaca 180
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ttcctctggc tctggagggn ggagaggaag gacttgcttt acccaagggt ctataaggaa 360
tcttgggaaa gacactgccc cttaaatcac tttttgggca ctggtgtcac ctttgtgtca 420
cttgtgtccc t 431

<210> 105
<211> 414
<212> DNA
<213> Homo sapiens

<400> 105
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gacaacaggc agcaccaaaa gcagggncng gaggactaag gacaactgtg ttgaaactga 120
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gaggacatta atgctagcat gcaatctagc cgtgtttgga tttaagacag aatttaatct 300
tcttgcctcc tttcctttcc ctcctcccct tttcagncct tttttcctta atacacaagt 360
ctcttttatg gagttaactc aagctatctt aaacagcatg aactaataaa ggca 414

<210> 106
<211> 435
<212> DNA
<213> Homo sapiens

<400> 106
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aggatgaaga cctttatgat gatccatttc catttggtga atgcctcttt caaaagaaga 180
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ttagaattta ggaca 435

<210> 107
<211> 437

<212> DNA
<213> Homo sapiens

<400> 107
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ctgattccca ggcaccacat gctgatgtgg tcaggaatga gatggcacct accttctgcag 180
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ggnggtttgc ttaaatg 437

<210> 108
<211> 383
<212> DNA
<213> Homo sapiens

<400> 108
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<210> 109
<211> 79
<212> DNA
<213> Homo sapiens

<400> 109
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atcctaggc attatatat 79

<210> 110
<211> 473
<212> DNA
<213> Homo sapiens

<400> 110
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aatggcgctg aaggcctagc acanggcagc ctctacctca aagcaccatc ccgcttaaca 120
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<210> 111
<211> 417
<212> DNA
<213> Homo sapiens

<400> 111
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<210> 112
<211> 262
<212> DNA
<213> Homo sapiens

<400> 112
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gaaaccaaaa gaaaagttcc catccatttt tctttccacc aattcaaaga ctaaatagta 240
gtggcttaaa attataatgt tt 262

<210> 113
<211> 229
<212> DNA
<213> Homo sapiens

<400> 113
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gcttaaagct taaatgatga atcagaagag ttatgctgta ttctaatgct gccactaggg 120
ccacacaggg tgccaacatc caatctcaag atcttcggga aatatgctca ccctccaaaa 180
tacttacaga tgtgtctcct ctttttgta aaataaatgc tcttcttat 229

<210> 114
<211> 318
<212> DNA
<213> Homo sapiens

<400> 114
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ctgctgagcc tgtatgaagc tactatccca ggactgtgaa aagtagacta gttgaggaag 240
aattcaagtc gacactgaac tagtggtaga gctctcatca tacagatcgt tggaaagtag 300
catcccgaca gttctgag 318

<210> 115
<211> 426
<212> DNA
<213> Homo sapiens

<400> 115
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ttccagcgac ttttacttcg ntcacgggca tatccacgcc agggctgcag aagcatttca 420
aaaggg 426

<210> 116
<211> 229
<212> DNA
<213> Homo sapiens

<400> 116
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actggagaaa aagccaccat caacccagaa ggccaacttc cataattata tgaatcgttt 120

gtgaacattt atggattaaa atgtttgagt aaagctgaaa tcggatatta cagtccatga 180
atagttcatg ccatgagaca aaaaattaaa gaaaaaaatt tcattgatt 229

<210> 117
<211> 430
<212> DNA
<213> Homo sapiens

<400> 117
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gcccaccccc acttggctgg aggagcagca cattccaccc atgctgagag ccactggttg 180
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ccgggtgagg gctgtcactt accacctgga ggacctaaaa aaggcgtcag aagcattatt 360
aaacgaactt gaaaaaggcc cagtggggca agcttntggg gctggcatct tganccagtg 420
ggtgcttggc 430

<210> 118
<211> 435
<212> DNA
<213> Homo sapiens

<400> 118
cnaanctnna aagggcncnt nccaggttaa aaccccncann cccaaaaaaa atngggttaa 60
aaggctgncc ttnggctcca tcaacactct gctagccaac actttggccg caagttcact 120
ctgctatcca cagctctggg gcacttctct ggctgtctgt tagtaaccac taacctaacc 180
caacctcatt ggccaggtaa aagctatcga aaataaactg aaaattgcta tctctatatg 240
nccatgaggn ttaatacagg aaaagctgat agtcaaaagt caagntcaaa tggcatttgg 300
tctccacagt gaaaaaatgn ctttangctg gaataccaaa gaactnggga ggcaacaccc 360
ggacctgnct tcaaaagatt ttnatcttcc cttttccctt ggntggcagg gcctaaaatc 420
aattcccagg gttca 435

<210> 119
<211> 405
<212> DNA
<213> Homo sapiens

<400> 119
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ggttcccctg ctactcttgt gaagtttcca ggtaccaaaa gcaaacttcc tcctaacgac 120
tcagggttcc aatcttttct cccttaaaaa tacaagatcc agaagaggag ccctgtcaga 180
tttccattca acaaaaccgn tgggcttacc aaccttacac tggaaacaac aagctcaaaa 240
gtggactctg aaacttgctt tttaaaaaaa gcgtttcaag cgataagtgt aacgtgctac 300
agcaagttta gacatctgca ggtctgatgc agtcatcttc tgggggggttt acccaacaga 360
cacacacagg gccaggcacc ttttcttctt tagcagcaga agaaa 405

<210> 120
<211> 424
<212> DNA
<213> Homo sapiens

<400> 120
gcgctgaccc acgaatgcaa ctctcagccg agctgtccct gccggatttc aaacagctga 60
agaagggctg ggagaacatc aaggcttggg ctaaaacaat tatggcccat gaaaggagag 120
agaaggtgaa agggagcgtc ancccccctcc tgagtaacca agtcctaggg aaggagatca 180
ccancatgct gctggagcag ctctacttcc tgcagagcac tccttccacc cctccccccg 240
gaggaggagc ccaaatacca cgccacggcc caagaatcat ttgctgtttc aaatagagaa 300
ctgggcgatg atgaaaaaag aagttcatac cgtttttcca acaccgtgaa aaggacctnt 360
taaaccctga accctcgtgt tcaagcttgt naagaataac agccaataaa aactacattg 420
agcc 424

<210> 121
<211> 422
<212> DNA
<213> Homo sapiens

<400> 121
nnnaactgaa ataangaagg atnggtcaga nanacagcca acggtgtggc caacaatcac 60
cactccagag ccctgcccca tctagggcgc acgtgcatgc ctctgaattt cctccccttt 120
ccttggtcca accacagtcc aggaaagcag attttctatg ccccgtggca atcacagtgg 180
aaaatggaag tacaatggag tgctgtacct acccaagcac caggaggcag gagtcgagct 240
actcacagac tccctagagg agaactccac gcacccaaac tctgctgtgc cccctctgag 300
ttctgagcat gccaggtgag gcctctccct ctctntntnc cttcattcca agtttttngg 360
aaaanaaagc aagcagcccg cgtgaccaga cagagccttc cttgctaata aacccatcct 420
ga 422

<210> 122
<211> 409
<212> DNA
<213> Homo sapiens

<400> 122
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ggctgnanct tggctcttga gaataangca ccaangaaca tgggagngca gcaaagctca 120
tgacattaca ggaggagcag agttctatca tgtagaaggt cattcacccg agcatgcttc 180
cttatcatca tctcatcttg tgccggtata caagtaagat cagccagctg ctgaaatctc 240
taaggaatat ctctccatgg agacagagcc agacggccca agtctcttct ctgttcttga 300
gttcctgttt tcaagtaatg atttggataa actgggagaa ccagtttcct ttcctccaac 360
tctggcaagc tgaaattaat tctccaaaga ctcctctttg gaggcaagc 409

<210> 123
<211> 419
<212> DNA
<213> Homo sapiens

<400> 123
gcgctgggga gctcctgctt taagtnanan cngaaatcac ccangtcann aagganaang 60
aaaatanaag ggcaanctcg ctgtaaagaa nggattactc aaangtngaa ccaaagccgg 120
gggaaagaac atggaaagca gtggagaggc accaggcagg tcgctttctc tttctggtcc 180
tcaaccacag cactgccgtc ttcagaacag taactattac ttgtccatac caggcatctt 240
caatactcct caactcatat caagaattct gcccagtcta aacagacctc catcctacaa 300
acactgaaac cctaacccaa aaccttacat atatccacct ctcacttatc ccttctgaga 360
cantatgaaa aacaaagngg cagtttccct tactggaata agtattaaat tttgcttgg 419

<210> 124
<211> 410
<212> DNA
<213> Homo sapiens

<400> 124
gagccgcaaa gacagcctgg aaagtgacag ctccacggcc atcattcccc atgagctgat 60
tcgcacgcgg cagcttgaga gcgtacatct gaaattcaac caggagtccg gagccctcat 120
tcctctctgc ctaaggggca ggctcctgca tggacggcac tttacatata aaagtatcac 180
aggtgacatg gccattaccg tttgtctcca cgggagtgga aggcgccttt gccactgagg 240
agcatcctta cgcggctcat ggaccctggt tacaaattct gttgaccgaa gagtttgtag 300
agaaaatgtt ggaggattta gaaagatttg acttcttcca gangaattca aacttcccaa 360
agagtacagc tggcctgaaa agaagctgaa ggtctccatc ctgcctgacg 410

<210> 125
<211> 358
<212> DNA
<213> Homo sapiens

<400> 125
cnnanactga gagataggan ctcgctacgg ttgcctggtc tcaaactcct gggcccaagc 60
catcttccag catttgcctc ccaaagttct gggattacag ggcctgcaca ccaatgaaac 120
tactgatatc agctgttctg aagaaaccca gaagagactg aatcaccaaa gagtgcagtt 180
tccacatcct gatgatttta tcatccttac tctgaccaaa cagtgacctc aattttacag 240
cccctcacac cctataatca tcctaaaaac ttcagcccag aactcctcag gaggataatt 300
tgagggtttc tcccatttcc ttatttggct gccctgtaat cattaaacac tttctctg 358

<210> 126
<211> 488
<212> DNA
<213> Homo sapiens

<400> 126
gtctggggag ctcctgcann annentgnac tgagagttgg ctnangagaa gatcaagagt 60
gccatctgga agctcagggc natgagaaca acctgggccc tggtctctca agccaccatc 120
aacccaataa tcaacanaaa cccagagggg aaacgacctc ctttcagcan gactgggaaa 180
cccttgaagg caggaactga gccttcattc cagcactaac tcaacaaaca tttcctgagc 240
tgtccctgaa gccaggccct ggctgagaat gctgaaaaga ttcagagcag atacacgtgg 300
gctctatcac acaaatttca tccatgtgtn ctacccaagt gataccactt gctctttctc 360
tgggctnccc cagtccctga cacagaactt tttggtcacc aacctaatca ttcanggatt 420
ataactgttt acatgtcagt ctcctctctt cgtcccctga cagcagggat atggntggcc 480
cttaatgc 488

<210> 127
<211> 437
<212> DNA
<213> Homo sapiens

<400> 127
gtgaggncac acgtgnaaca acacgntgtn tgtgaaccat gaaagggagc ttcgacngac 60
accnnacctg ccacagcctt gatcttaacc tttgcngaag ncacaactga gagannatnn 120
nnnntgtggt ttataaccca nccagtntat gatatttntgc tncannaacc tgaatggact 180
aagacnctcc ccaccatgan aatgtccaaa cataatgnga cagatgtctt tacatcantn 240
gtggatgctg ngacanaggc ntttacaaac acagagcaac ccagggagct gatcagcatg 300
aatgaggctg gaaggaggct canaaatcc atctttccag tgaacttgga acaccagaaa 360
caagtggagc anaggggaga gaatntcttt gaaaacgcag ttgggagaca gagccangta 420
acgggaaaga aacaagg 437

<210> 128
<211> 438
<212> DNA
<213> Homo sapiens

<400> 128
attaaaaaga aaaaagaaaa tcaggtggga taaagagcct caggtctaac tgaattgtca 60
actaatgatg gtctgagagt acctgtgctg aaatggaatt gtctttgagt ggacacttct 120
tagatgagac ctattgtggc caatagctcc tgaggaactg aagccttcag ttcaaaactt 180
gtgtgagaaa aatgaatctt gccaactact ggagtgagct tagaaatgaa tccatcccca 240
gttgaccctt gaatgtagcc ttgtcagaga cccagagaca aagcatcctg ctaatctgca 300
ctgggttcta ggcccacaga aaccatggga taataacttt gtgntgnttt taaccccttg 360
aaaccaacca aataaaatcc ttaagatgtt cccctgngga agggttccat tggcagggat 420
ctgcacttca caaccaaa 438

<210> 129
<211> 442
<212> DNA
<213> Homo sapiens

<400> 129
ggcaaattaa cccagaagag tacttcagag aacacagaca aactgccgtg cagtgaagag 60
aatgtggcag gaagccctgg tattctagaa gaagctctgc ccactccaga caggatccgc 120

acgcctagtg ccatgtctat ctccaaggag atcacattct agagccaagg accgccactg 180
agaagaaagt aaccgtgagc cgtcagaatg catacctgga gcgctccagg aaggaaatct 240
cagccccggc atcctccatg gtcacacgga gagggcgggt gtccttgtag ctttggccct 300
gagatgggag ctagagctgg acacagggtt ctagtcctgg cttttgtgga aacaagttcc 360
caaacctggn gcaagngcct tacctgtctg ngtaatgggg ggagctgatg tggatcatct 420
ttaagccctc tgcaagatgg ag 442

<210> 130
<211> 440
<212> DNA
<213> Homo sapiens

<400> 130
gaggtggagt cttgccatgc ccttccatta caaaatcctc ctgttccacc tgcaaaggca 60
agcaccacag gtcagcagca gtcagtaact acaatgcgac tcactccaag aacccacacc 120
tgccctgtgc agaaccacag ggccgtttca ctgtggggca cagaacagaa gcctgggcca 180
atggttttca aacttctcct tgagtgatta gatctgcaga aaaaaggaaa catgttgatc 240
ggcaaaacac ataactctga caaaggatta gcatctagaa tataaagaa cggtgatgaa 300
tcaatgagac aaagacagcc tactagaaaa atctggaaat aacccaagcc gggaatttcn 360
ntgaagagaa cacataancn gttntaacat atgaaaagat attcaatctt atgtcagtca 420
agaaaatgca aattaaaacc 440

<210> 131
<211> 434
<212> DNA
<213> Homo sapiens

<400> 131
gaagaaaatg ttaaaaagta ataaccaaag aaaaagtcag ccaactccca cagcctggtc 60
ttgctgtgct gaatggcaga gaagatcaca gaggaagaaa aaagaaaaag acagaaaaaa 120
ggaggcggag aatttcttgc ttaaactgga cctagtccag ctggcaagaa gaggtggttt 180
tcttaacgcc tgcaaaacct gattactttt tttaaaggaa tgaagaagaa ggagatgtaa 240
acacagccat taaaacagat ttaaggtact tagttttaat ctagtctaag accttttcaa 300
ttgtatgctg ctctgcaatt ctctgcttgc tagacattaa tacngngcat aagcccntgg 360
tcagngtctt ttaaccagng aacgctttca gctgagctct gnggttaccc tctcaggtca 420
ggcatggaag gcct 434

<210> 132
<211> 437
<212> DNA
<213> Homo sapiens

<400> 132
gtaaacccag ttcactcagg cagaagcaag aggaagaaca ttcctccagc tcctcctcat 60
gcaggcccga gaggtgggag ggcattctgc cagcccagta tatccacttt gcttcgacaa 120
atgtcagcct gcccagaata aggaagtacc cacagccggg aaaggtaaat ccaaaccctg 180
aaaagacaga tactgagcat ttgaaataac acagcttgca gcgtccttgc ggagccctgt 240
ttatggggca ataaaccatt taaacgactg tgtgttggaa cccacaaggt cgccttgaaa 300
ggcttttcac agacactgct agtagggctc caggacctct ngaaggccna gatngggggg 360
nctttttgct tntgcttgaa gcttgntggt tcccctccat cangaacgcc agcccctgga 420
gaggctgcca tgagaaa 437

<210> 133
<211> 341
<212> DNA
<213> Homo sapiens

<400> 133
gaagaaacac aagatttaag gttgtttgtc aactgacagc cctttctatc aacaactaaa 60
taaaaaaatc tgtattccag aaacatgaca cttcatgtac cacccatttt cctcataaga 120
aaccaaaagg tgtccatgac ttaggtacta aatggcaagg ctggaaccag aatccaagtt 180
gcccagtcac acagttttgg tttttaaata accaaattgg tcaaaaatct tcctcaaaga 240

caaaaacaga tgaaggtaaa atgccaattg gttaaattta aacagagact tcactttgtt 300
cttttcaggt tcaataataa acaattctag tgattagcat g 341

<210> 134
<211> 442
<212> DNA
<213> Homo sapiens

<400> 134
gagtaaacga tcccaattgc agtatatctg nggntcatct ggcttcttct cacaccacct 60
ctgttgacat gggaggcctg ccggccacac atccaggaag tatgaaatca gcggggttcc 120
tcccttctt gctccaggga agcctgagag ggactctgca gattgcattt ggaatccatc 180
tgccagggag gggtaagaag aagcagagtg tcaccgggta agagtcgaca gttttgaaga 240
ctcgtagctg cgaatctttc aggaaataat ccagaacagt ctcctcgctg gacaggaaag 300
gaaacctatc ctagagaggc gaatcctctg tcctggaccc ctgccccana aaatgggtca 360
ggggaggga ttntttgggg gngtttcnac ctgctgcttg cagggcttcg gttgccaaga 420
gtttccccaa tacctaaacc cc 442

<210> 135
<211> 434
<212> DNA
<213> Homo sapiens

<400> 135
tctccatgct ctggatagag gaggttcaca agccagggcc tgaagattaa cagagctttg 60
aagccaaaag gtgacccctg gaccatggac ttcgcacctc ctttcttaag ggctttaaaa 120
tagaaaagaa caggagctag aagatgaggc agaagtcgag gacttctgtt tttctggaag 180
gctcctctga gccaacaagg ccagggctgt tctggatttc agagcacaaa gaggctcctg 240
gagccagcca tggtctcctg aggcttttac caacttgaaa gcagcctttc tccagggcag 300
aaacgaagca tctccccagc gctcgccatc ctcagctgnt ctttacaaca agaactttac 360
aaggatgccc ggatgaaggc ccaananacc cgcgttctgg gcaagccact tttaccacac 420
cgactggatc cccc 434

<210> 136
<211> 433
<212> DNA
<213> Homo sapiens

<400> 136
gtacctaagg cagtaaaccc ccaactccct ggaagggccc actgggcgct cacttcgctc 60
cagagcctcg cctggtttcc gcttcgggat ccggtcaccc aacccagctc tccagttgct 120
gctgtttctc gtgagactgt cagagtgaag gggtccaaag ctccgacttc cagcctcaga 180
aatcccaact caggcaggat cagcgaagcg tccctcgcag tggctggagg gagagccagg 240
cggggcccag gctgccactt atcagggctg taaatgccac cctgaggccc acgcctgcca 300
acactgctcc ccacaagact aagtcctgca gcctcagccc aaaaagaacc gggcctaacc 360
ccaaaacgga nggtcatgtt caagccacac cccagtgaac cctggcgacc caccccacag 420
tgccctgccc tcc 433

<210> 137
<211> 443
<212> DNA
<213> Homo sapiens

<400> 137
gactagaact attgccactg aggggcaggt gggaagttca gccaactcgg aacccggagg 60
ccccacctta cctccctttg tgaagagccc agagcctttg tccaaagctg catcacttcc 120
cacccagccc ttcctgagcc aactccccga tgtctccaga agaacacagt cggcatcatc 180
gtgataacat cagggaaact cctatttcca gcagtttctc cttcagctgc aaaaatgtgc 240
agcagtagac agggcgtggg tttttgaagt ctctgcagga ggtagagtta ttttctcagc 300
accacatctg agcgcatctt ctaagggtgg ccgactgtgt gggaactgca agagcttaac 360
ccgggatgca agccctccca ttccccaccc tgtccactac caccacgcct ggatccgaca 420
ggcagggcag gaccccatgc ccc 443

<210> 138
<211> 405
<212> DNA
<213> Homo sapiens

<400> 138
gctctgggga gctcctgcat tannncntan ctgagtatca tccntctgcc atcaagaatg 60
taagtatgaa gaatgttccg acactgctcc aggactgtct ttcaagccac tgacaaccat 120
cctgcaaatt ttgatactgg tgcctgtttg gtgtccctag aggatctaaa tgaagatgtg 180
aaaacaacaa ctaagaaaat attttaaatg gcaattactc aacacgagaa gttaaaacaa 240
tgtccacact gagactgaaa tgacagcaac agaaacagca agtcagagcc atgcctgtac 300
aatgacaact agatcaaaac tgccacctgg ccaaaagcaa tactcagatg ctattaactg 360
taagacagtt aatggtatgt tatgaggtga aaaaaaaaat tcctt 405

<210> 139
<211> 448
<212> DNA
<213> Homo sapiens

<400> 139
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gaatgagaag cttccagcaa ggcagctgct tccagcagca agctcctgca tagcccacag 120
gccattccag ctcaatgctg gagaagaatc ttccccctaa cagcactgcc cagcactacc 180
caactaaggc ttctctggtt aaactgccca aggatgccca aagaacttgt ttctaaagga 240
aggaaaacag atgccaagac ttcttgtgct ttctccaggg ggctcagagc aggccctgat 300
cactaccctg gatgcacaaa gtatctatca aattcccaca aggtanaaag ggttgccagg 360
aatgggaaga aacttcaata ttcgaagtca ccaatcacag aagataactg gcaaaacagt 420
tctactaagc aagcacagag ccatttgc 448

<210> 140
<211> 458
<212> DNA
<213> Homo sapiens

<400> 140
aactgaggtg gtggtggtca agagcaaggt cgaggctcac ctgtgcccat ttggttccgt 60
acattgctca ctagaggcat catcgacaga gtatgaatca gctccccaat tagcctgacc 120
gtaatcacct gtgttgcttg attattatac aaattccccg acctcatacc gacctactga 180
atcgaaatct ctaggagtag attctgggaa tctgtatcgc tggtaaagct cccaggtgat 240
tcctataatc tggcaatgtg ggagacacga gcattaaggg aacccagcaa caggctccat 300
cctctgccta acatcagcaa cctcagcaga gacttggtcc cagggaccct tgttccntta 360
tgtaccccaa gacactgtcc ctaaatggng cacaaaagca agactcaggc ctgtctcaca 420
cactggcaaa gctgctgccc cccagctcaa accagctc 458

<210> 141
<211> 451
<212> DNA
<213> Homo sapiens

<400> 141
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gtgatgataa caaaaagcaa taattgatat ctgaacaaag attcttgggc agccgagccc 120
ctcttgaatt cctcagccta ccatcatgat caacacctcc catgttccgt ccatgaatga 180
ccgcactgac agcactggag agatttaatg ggtcaccaat tgaggcagtg aaggcactca 240
tggcactcag agctggaatg gggctgatct gagttgtact gttgactgca gtggtgatga 300
caacctgcat tcctttgctg gctgcatcga caactgcttt gtnaatgggc attntaccgg 360
aagcatcacc tggggccacc cacaacgagg ccatncttca cctgttgacc aagagatggg 420
tcaatcctcg gttgcaactc acaaggtgtt c 451

<210> 142
<211> 450
<212> DNA

<213> Homo sapiens

<400> 142
atcccttctg gagctggtcc taattgcttt tcacaggagg gatgcaaact ggaaagttcc 60
tacctattca gcgaaggcac tccaagtcct gggctctttt ctcctcgggg gcaaagatga 120
gacttctctt ctgtagagat cacaggtgca tctgtacagg ttggagtgct cccccaaccc 180
tggacccctа ggagcggccg tgatttgtga cacaaggccc cacccgttga tctactcttc 240
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agggagaacg ccatgtggag gtgaagataa agaacacaac ggtgcttntt acaacccaag 360
gaatgccaag gacctccagc aaaccaccaa gaagctcagg gggaggcaca gaacgaattc 420
tttctcacag acctcagaag gaaccaacca 450

<210> 143
<211> 452
<212> DNA
<213> Homo sapiens

<400> 143
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caacccctgg gcattccctg ggcactaccc agcaaagccc tatctttgca tcggtctcag 120
aaggagtctc ccagatgctg caccagctgc ccagcgctgc tggaggaaat ctccaccgct 180
gcagaaaggc catccctcca ctccctggac agccctctcc acgtcaccca cctgggtcct 240
ctcctactcc ctttggtgcc tggtctttcc cagcagctgc ctacccccaa ctccctgcta 300
ttcaagccct gnaggcacct tgactcctaa atgaatgaac ttaactgctt gccctgcccc 360
cttattgatc tgccagggtt tccacccttn catcttnttca gggcctgcct ttgcagcaca 420
agccaggctg ccatcacctc atgttccaat ta 452

<210> 144
<211> 258
<212> DNA
<213> Homo sapiens

<400> 144
ctgtcctgag agcacgtctc tacatctcta cctgcattct ggaatcaagg ggaaaaggcc 60
aaaacggaca agaacactag aatcagcccg tgtcccaacc ctttgactac aagggacttt 120
tcccgcctat ctgtggtggt gggtatcatg aaaattatgc acaaaccttt ttttttttta 180
anctcatcan ctntngttag cattagggna tttnatntgg ggcccaggag cattnttttt 240
ccaanggggc cctgaaaa 258

<210> 145
<211> 445
<212> DNA
<213> Homo sapiens

<400> 145
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cgtgtcctcc aagggtttca aggttatcgt atgccctgaa attgggcaag gagctttaag 120
agggaacttt gagtttgcca gagaaaactc aagatgtttc tacatgaaga aaatggtttc 180
agacatttga cttctttaat ttttgcatac tctttgtgat ggttgttagc aaagacctaa 240
agtggttgta tggctatttg caaaggctga gtgtgacttg atattggctc aacttgaaaa 300
ctttgatatt tgatgnttgn attcaaaatt ggaaacaaag gnggttaaaa agggnggata 360
tatgaattat ggggggggcat ataanacttt gcagaactta cctgcnncctt atatattttc 420
tgccaaaata gntgttggtt tgatg 445

<210> 146
<211> 437
<212> DNA
<213> Homo sapiens

<400> 146
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attgccctga aataatatgt gctgtgcctg cctctgtaca gttcagctca cctttgagac 120

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atttcgttgt gtttgttcca acagcggtca attgtgttgt atttacccca gaaatcactg      180
ctaacaccag cataccagcc gccctttctc gtgagcttgt gagtggttta cggagcagaa      240
aaagagttaa tcgatggata tgaattaaac acaggaaacc agcactagag gaacctcaga      300
ctccaggcct aaaaccactt gtgactggag tgacgttaat cacaaganaa gggagcctcc      360
atggtaacag gatgctgaaa cctgacacat acaaggnact atgcactttt caaagcactt      420
acatttgatc actcttg                                                     437

      <210> 147
      <211> 453
      <212> DNA
      <213> Homo sapiens

      <400> 147
gcttcagttt aaaaggactg cctgtcctag ctgggattgg agaattgaga gaaaggcatg       60
tgatcctccc gggacccaga gagatcagca gaccagaagg cctacatgta cactggaaag      120
cccccaaccc aggaatccct gtacgacttg aggcattatc tcactgtgca tggctgaagc      180
ggtagatgcc atcattaccc tcatttcaca cctgcagaaa ctgaggtata gaaacattaa      240
ctggtctagt cacgagggat tctgtgatgc ctgagacata tgacctgccc tccaagacca      300
taagtgacag accaagaatt tgatcccatg tcctggnggn cccacaagnc tggggccttt      360
accattanag caggggtttc ctctgggggt tctcttgtcc ccaggggaca tttggcaaca      420
tctggaaaca tttttcgttg tcacaaatga gct                                   453

      <210> 148
      <211> 451
      <212> DNA
      <213> Homo sapiens

      <400> 148
ctgaagagca ttgaccaagt tattatcttc aactctctca aaggggtgaa gagagaaaag       60
caacactgag tcaactggct ggntttttcat cccttttctct tcttcagttg tgggctggag    120
agagatgtaa ttccaggaca ttggccagcc ttttgttatg tggatacgct ttacacaact      180
acagtttatc catcagaatg aaatacagac aaaagctgag gaaatcagtc ttcttaatag      240
atagaaagtg atcctttctg cctccaaata aaactgaatt ataacattct tcgtatttct      300
ctgggtacac atctggttta aaaattagaa gttaaatttt aaaagtaggc agaaggtttg      360
gtttttagaa gaaaagacat tttaactgta atagnggatc attattttaa tgcttataaa      420
gtccaatcaa agataaatgt caaaccataa c                                     451

      <210> 149
      <211> 351
      <212> DNA
      <213> Homo sapiens

      <400> 149
cnaactgaga aaagcaaaag atatttgcca atgaacaata acctggatgc tcaaaggatg       60
ataaccctga ggttgaggga taccaagtac cttgtccaca attcagcaac aatgggacag      120
gtgtgataca aacctctttt tccatcttgt tctctttctg cttgaccatt gcaccattga      180
gagaagtgaa acttgggctg agtctacaag ggcacccaa aataaccatg gtgtgtttat       240
gttcatttaa aatcataaaa tttgtgtagg aaataaaaaa aaaaggccng cgaggccnat      300
tcagcttgga cttaaccagg ctgaacttgn tnaaaagggg gggcctccca a               351

      <210> 150
      <211> 244
      <212> DNA
      <213> Homo sapiens

      <400> 150
ctctggggag ctcctgcatt nctacctncc ttnagatana nctgnnggct ggaatgtana       60
agtggacttt tggccacgtg gatgaggaat tgaagcagtc agttctgatc tagagatgga      120
aggcgcctgc tgaggacagc agggctgctt ggcaccctgg gtccctgaat ggctctgtgg      180
agcactgcct gatggcctac cctggactgt tgcctgagac agaaataaac ttttatcttg      240
ttcc                                                                   244
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<210> 151
<211> 573
<212> DNA
<213> Homo sapiens

<400> 151
gttttcaagc aaantggcng taattggaag aaggnaaaac gcccagggtg ccttaattta 60
gggnccgtgg ctccnaaagg tnattcggtc cccgggtttc ntcaacttgt ngaatggatg 120
gaaaagcaat gngtttacca tttgggcgga aattttgaaa aatcattgga tggaccacaa 180
gaagcttggg ggaaaaaatt tgttgttggg aaacctcaca agggcaaggg ctaaaacaa 240
aggttgtggg gggggtggga tcaagcccca agaatttga ccgtngccaa acctcaaaaa 300
gaccttggga aaaaaaatgg gccaagaaat aaaatcttgc tttccatccc cgcccaaggt 360
tttgggtttt caatttggta cttggaccaa ccttcaagct tgggcanttc attngggacc 420
canttgnaaa gaaaagccan ggaaccgaaa aaaacccccn ccnngggang ggggaaaaaa 480
atcctnnggg gaatttcttt tttttnttaa gggggatggg taaantacca ttattatttt 540
taccnaaaat aaaaaaatgg ccctcatggc aca 573

<210> 152
<211> 845
<212> DNA
<213> Homo sapiens

<400> 152
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cttggccttt tattgaagct tggtaancac ttcnaccant ggaagggggt cttggcaagc 120
tttcacttcc ttggaaagcc caggcggaag aacccacaaa aaccccaccc gggganggaa 180
atgaaacaag ctggcaagga acgccgccgg ccctttaaag atgcctggta aaccacttca 240
cccaaggaaa gggtcccgca agctttcact tccttaaaag cccaagccga agaaccaagg 300
gaaacccccc acccaagaaa gggaaaaaaa aactcccgaa acaacatctt gaaaccatca 360
agaaaggaaa caaaacctcc cgggaacacc gccttgccct tttgaagaaa cttgtgaaca 420
cttcaccccg tgaaggggtc ccgccggctt tcatttcctt gaaagtcaag tggaagaacc 480
aaaaganacc cacccaaatt cccgggacat tgtttccttc actttccttt taataagctt 540
aatttaaaat ggtgaacttt ttctcggagg ggttgggctt tttggaccat tnctttggg 600
gaaaacaagc acttccttaa tcaaattggt caccctttnc ccttgctttg gggtttttgn 660
ttatttaanc cactttattt gggccatctt cttggggcca naagaatttt attaagccnc 720
caatttaaaa tantcccatt ttggcttacc caagccttcc ctttcattat taacccccct 780
tgccccaatt aangcaaggg nccccttata aaaccaaaat nnggggcttg nggaggccaa 840
aaaaa 845

<210> 153
<211> 582
<212> DNA
<213> Homo sapiens

<400> 153
gtgcctgtct gaaaaccagt tcctctatga ctgtgatctc caagtgatca aagtcttgtc 60
ctggaagcca gactagtgat atgcaccttg taccttgctc ctcaaggcac caacaaatag 120
gaatccagag caacttttctt agctggagtg gcttctatgt ttctgactgg actttcacgg 180
atacaaacag tggggctctt tgcaaaacac tcttctaagc tttcagaagc aggtcataaa 240
gccgaaaagg acatttctgc ctttctctga agcaggtcat aagtccctca ttagagaagt 300
atcctccta tacctgaaga aaaggaacat ccttatctat gaagacacag gaactcagag 360
aagaatctga acaaacaggc cttgcaaaat gccctccagc ttcctgccat tagatcatac 420
ctccttttc cggccatact tctccataac tatccacttc ttcatcagat ctagcataaa 480
aacccatctg gtttactggn tggcttgggt cttcatttnc ttatgaangc tccgcatacg 540
taaaaacnta cgttaaaaaa aatggggatg cttttctttg gt 582

<210> 154
<211> 627
<212> DNA
<213> Homo sapiens

<400> 154

atgcatcagc agaacctacc acacggcacc tactgcgggc ttcagttttg ctgtagaacc 60
gagaaacatc acgttagatg ctttagcaac aacaatgtat atgttgcata gaagaaaagt 120
gtcccagaag aacagccagc tgtcctttac atgaaattgt ggcactgcct gtaagaagta 180
tatccaatga gaacttgtcc tcaccatgta atacttttaa tgggtgagcc atttcaacac 240
tttacatact gccgagtaag tttctacaga actttctcat tgtactcagc gctgtctgtg 300
cagttaattt aggcatcaga aaactcagtt gttaattttc tgacttgcct ctggactctt 360
aaatgctatt gctccaatca taacacgtcg gaacacttac gcagatttca acaataatat 420
ccacagctgg gaataaatca aagcaggttt atcactggat aagtgctatt ggaatatggg 480
taccaagaca acatgaagca aaggacagat ttcactttag aagattaaga cagagccctg 540
gggggggaaaa aaaagaggta atcccaacaa agtctatgca accnttaaaa aatattattc 600
agagcagaaa tgcagaattg gcctttg 627

<210> 155
<211> 598
<212> DNA
<213> Homo sapiens

<400> 155
caaaactgaa aaactggntg accttncgct tngnntncaa caaaccaaga ctagctttga 60
ctatgacaat nggtatctaa ngaatgccag acaggatgga tgaagaccag gacacaactc 120
actccaccaa actgtgatgt tacgtcattt accttggtcc ccacccactt tgcctttgaa 180
tgaagacgtg tccccagcnn ttgganaacg agaaggaaac acgccaaatt aaggtcnnat 240
ttacatcaac agagaatata gaggctcaag agaggaattc acttaactta taggaaaacg 300
aagtcatatt ttggcacatc gagtttgtag tctttgagaa atgaaaatcc tcancaaaaa 360
gcttttgtct gaccagctgt gaggtaagaa tgtgcaagaa gtcaaagcaa gcgaggaggc 420
ggagccggta ctgtcctgga aagcaaaacc cagaaaggtg gcgaatctgc tccaaagctg 480
cctcttttct gctcctaagg aagatgcntt ctcangatac agggattttg tgtatgaaaa 540
aaaaatggcc atagctgctt acagaanaga atgggtggna atgccaattt ttgactat 598

<210> 156
<211> 284
<212> DNA
<213> Homo sapiens

<400> 156
aacctcaggc caagtgttct tgacagctca tccacagact cccactggta aagcagcatg 60
aggatggctt ctgttatttt atttcagaat tttttcctgc agtggcatgc cagtaccagc 120
tgaggatcat gtatgcaata tttgccttct ttcatcttct acctaggatg gctttaattc 180
tcttcgagga gaatttattt tagtttttcc cagtaagaga atccacttct cttgcccata 240
ttcataaatt atcattaaaa attaaacttg gtacaataaa tatt 284

<210> 157
<211> 759
<212> DNA
<213> Homo sapiens

<400> 157
ggctaccctc gtgntganat gaatnaactg gcncctggng gccgaaaagc gaggngccnc 60
tttgttttgg gagggnnccg taccccgcgg gaaacccttt tttgcccgaa ccaagcccaa 120
gcggaatggt ttggtcttcg gcctggccaa ncnaagcccc cccaagangg ggccaaagct 180
tcttggtgga aactaagtcc caccttgttg cgggaaggcc cgggggtcaa ncccaaaagt 240
ncccggnca nggccaagca atcggtcatc gggggcccta taagcnggga aaagaaagaa 300
aaagccacaa gncaaagtat cttggcttga aaaaaatggg ggggnntant aaacgggaag 360
tcttcgcccg tgtcaccaag gcttgggaag tgtgccaagt ggatgaagaa tctcagctca 420
cttgcaaacc ttcacctcct tgggggttcaa aagtggattt ctttcttggc ttcaaccttt 480
tcccaagtaa gcttgggaat tacaagggcc ccggnccacc atgcccaagt atttttggt 540
gggccaagaa ggcangggaa aanggaaagg ngggggtacc ttggaaaacg aacaagcttc 600
ttttcccctt ggggaacttg gnaagcaatt nccgaagcac caacaagtcc aaccccggcc 660
aagcctttt ggtttccttg gcacaagtct tggncntntt naaagaaacc aacnaacttc 720
cattattttt attggacgaa tnaaaaaaat ttgggtagg 759

<210> 158

<211> 501
<212> DNA
<213> Homo sapiens

<400> 158
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cntaagggcc ntntngncnn caanccctg acnaaactta anggagtccc ntcgaaaccg 120
gggccaccac ctttcttcac cttttgcaag gcaaggaagg cccggaaggg ntaagccctc 180
aagcgtcaac gaagttcaaa agancttggg ttacccagca agtttgcccc atctgctcaa 240
gggatgtggg ccttcttctt gatgaagtaa gttgaaagtg cttgggatgt gaaatcaagg 300
aactcggagc tcaaagttca atgaagtacc ttggaaaatt ggattgggga agctggccca 360
aggaaaatca ggaaagaaaa naagtcctga agattcaagg aagaaagtaa aagcccgcct 420
ggcttganaa tgggggtggg ccanggccaa accttgatca agggcccgag caaaacccgc 480
actctttcca aataaaagct t 501

<210> 159
<211> 736
<212> DNA
<213> Homo sapiens

<400> 159
gntaccnact ngnacccagt ggatnnatca ancacgaagc cctcacttttt gacntcttng 60
cannngngna aaatttggag ctgggatttc attgcccatg ggcaagatgg ggaananggt 120
tancctttgg cttanaaca aggangggaa aaacccaann ctttnaccan aaaagaaanc 180
ttggganattc tttgggggttc ttggaacang aaccggtttt acctgggcat ttttttttaac 240
aaaaacnacc ctttaacttg gcttatttaa cccggcctgg cttcaatcaa cccacccttg 300
gggccctggc ccccaagtgg gccaatantg cccttcaccc aacctattgg gcanttaagc 360
ccacaaggcc caaagaataa acttatataa tcaanaaatg gaantaagaa aagaaaaatg 420
tggttcactt gggaaaaact tggcttggtt ggaagcccct cccaatgggg gaagcttgaa 480
ggagcttgtg gtctcttgca aggccattgg ggggaacttg ggcccacaaa gccaaaagaa 540
gtcaagcanc catggaaagc ccccnggagc ttgtaaccgg tgtgcaacca aggccgccca 600
attccaaaca agcatggggg aaaccaacaa gtnggncgcc aaatcatttt nctcaattta 660
ttnggggcnaa aaaaggnngc tatttttttc acccttgggt aaggtggtng cnttttgga 720
gaaacttccc aaatta 736

<210> 160
<211> 458
<212> DNA
<213> Homo sapiens

<400> 160
aagacataca tcatgagaga gagagattac agtatgcaat ctctcagctg ccaacagaac 60
acagatgggc ttgggaacag agaatgatcc agatctgcag gactggagca atccgtggga 120
agtttggaca gaagatctga tgcataagac agtaaaggac tactgaatgt tccatgatag 180
atatgcttgt tcttttgcct gcatgccctt gaataaagac attttgatct ccaggaccaa 240
cctgagaaac atataattta atctagtttt gaaagaagag ccctgctaca caaatactgg 300
ctcacaatgt taacagatat caactgaaat atcaaagggc tttcatattt cattaaattg 360
actatcctat gtgtttgata tttccattta attgaatatt tcttaactca atgaaaaatg 420
tatgagcctg ctgtgataaa tcccgtgtcg catatggg 458

<210> 161
<211> 264
<212> DNA
<213> Homo sapiens

<400> 161
cagaaattga gaatcatttc acttttgggg gaacgggaag ctggttgtgn accaccctta 60
tgtgnacctt cctgtccttc agctacatcn gatgaacctt gggcagtgaa ttatctaagt 120
cccatccaag cttccagaaa gaactgcagc cccagctgac agcttgactg caacctcatg 180
aatgtttctg agctaggacc acccagttgc ttctgaattc ctcaccctca gaaaactatg 240
aatacaataa atgctgatta tttt 264

<210> 162
<211> 882
<212> DNA
<213> Homo sapiens

<400> 162
agtcaganac tngaagccca tactttccca attgccttcc aagcttgttt gcaccgggan 60
ggtttcaaca atcantattt ttccaagaaa nggcttcctt gggaaaagan ngtggaaata 120
ttggtggtcc ccaatccaag aaaanccttg aatgggggcg anttggtgaa ctttgggctt 180
gcttgtccat tcctttcaat ggtcaagccc caananaaan atctggtggt caagccccgc 240
cacaaaccat tacttggttt aaagccaagt ggggaatgaa aaagtggcca aagccttgcc 300
caaagaaaaa aatgggtaaa agggaaaaat gtttgccccc aagggaaaga aaacacccat 360
gggcaaagat nggaaaccaa gtaaaccagg gggccacaat caaggggggg anaacaccga 420
aaacattacc gggcccanta aaaacttcct ttaattaaga anannngtcta ccaagattaa 480
aatctancag atgaacanat tcctcaaagt tgggaacttt gggcccattg aatttgggnt 540
tggtcccttg ccattactng atggaaaact actggatggt ccaagcttgg gtctgaaang 600
gacccctcac ccagaaagcc ttaaattcan tcaaaagaaa atggcaaatt tcccattatn 660
cctaaatgga attcaaatct tccctttacc ccttggaccc caatcaaggn ggggncccaa 720
aaatttttcc caaccccct ttggccttcc ccaaaaaacc ccccaacccc caanaaaccn 780
tcttttaaaa aaaattaaag aaatctttcc ttccttaact ttccttggac ttcaanccnn 840
cccattgtna atccatttaa aacctcntnt ttgcttggaa aa 882

<210> 163
<211> 828
<212> DNA
<213> Homo sapiens

<400> 163
cagatactga gaacacaaca aaaagaacct gtcaccacaa caaagagggg aaagtggacc 60
aagtggctta tcttgaaacc ttgtgggtcc ttggggaagc ccaggggtga accctgaata 120
atgaacatct aaaaagaaag ccttttctggg aacttcttga aacaaagaaa tttcggtggg 180
ccctgccaaa agcttgccc aatttgccac ttttttcaaa atgccccttt gggaatgaac 240
ccaagccact tttaaatctt gaaaaccttg caaccaagaa ctaagcccaa ccacctgggc 300
ccatgaaaac tttgccccct ttcacttgga tctgggaact tcaacctttct tggancccta 360
acggcttttt aaagccaaag ccacttaact tggcacttct aacaagaaat taaccccaac 420
ttgggaatcc cttgggaacc caacaagaaa ttccctttca aggaatccct ttctttggct 480
ggccaagaat ggaaagccaa aagggaaatt aatttccccc ttcaaagttt ttctaaagtg 540
aatttccaaa aagccaaang nggnggggtgg aaaatttccc aagtaaccaa gaaaaccaag 600
aagggttggc cccaatagaa agtaantttt ttaatctaat aaccntcccc tttgggtacc 660
ctagaaaaaa ngcttatttg agaactaatg aagctccacc agaaccangg gcctttcgcc 720
ancaaaacct ccaaaatcaa taaattggga ccatggtttt aaatggatta cctggggaaa 780
tccntggata ggccctnnna aaaaggggga nangctaatt aaaacaaa 828

<210> 164
<211> 660
<212> DNA
<213> Homo sapiens

<400> 164
tggagaaaat gggattggga aacagaaggg agaagaaact gggcntttac cataagaagg 60
ttgcanaaca ccctttaaaa acctaacctt ttaaaatggc agtgggaaag cnttcaacat 120
ggaggcctcg tctaatttaa aacaaaccac acagacncac ttggcccaaa agcagcgact 180
ggcctctgaa gannaaaagg tggggccctg caagtactgg gctgggaacc acctccacat 240
ctgaaagaat gctgtttgcc tgtatttgct tcccaacgtc cttccttccc ttgcctggtt 300
gcctgttggg cctaacatgg agctctgccc acagtaagtg tcgttactat ggccactagc 360
ccatacccaag gcatggcctt tgcaagtccc caacatacag ctcccgacct cacaagcaag 420
nccatctcta ntgctggnca gaaagtaaaa gttccacacng ggcggggcaa aaagtcctgc 480
tcattccaan gnancaacgc accctnaaca agcttttccc aaaangcaac tcaaccactc 540
tttagaattt ttttttttt tnaaaaaaaa ccgggnttaa ggaacttggc aaaaaaaanc 600
ccccnagntg gaaaanccct ggggaaaaan tttctgggnc ccccccccgg ggctgaactt 660

<210> 165

<211> 643
<212> DNA
<213> Homo sapiens

<400> 165
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ggaagggaag angaacncnt ananggngc ntantttngc nncccaggtn gnccttcaat 120
taaaagaacc tttggcntcc agggttcaan gtggattctt tttgctttcaa gccttcccga 180
gtaagctggg gaactaacag ggtggtcaag gccttcttga ccccaagcct aaagcccatc 240
attatccccc tggtggatct tgcacctaac ccatcccaga atggccctga aagtaagtga 300
aagantcccc caaaaagaaa gtgaaaataa gccttaactg gatggcattc ccaccattgn 360
gaatttgttt ctgccttcac ccttaactgg atcaatgtac tttgaaaatc tccccgcacc 420
ctttaaaaaa ngttctttgt aattctcccc ancctttgaa aaatgtactt tgngaagaat 480
ccanccttct ggccgcaaaa cattgctctt aacttccacc gcctatncca aaacctataa 540
gaactaatgg ataatccacc acccttttgct tggacttctt tttcgggact cannccccgnc 600
tgnaaccccc ggtgaataaa aacaagnccc cttgtgtccc ccc 643

<210> 166
<211> 629
<212> DNA
<213> Homo sapiens

<400> 166
tcaganactn ggagngaaga acaagctttc ccaagggctt ggaaaagaag gggggaagtg 60
ccgggaacca ntgccttccn ccantaacca cttggcccac ttcttggtgg aacctttctg 120
gcaagcaaaa aaccctggaa acccccaaaa gaaggcaagc tttcttcaaa aagtaaaaaa 180
gtgggaaatg gaaagtttcc ctgggtggaa ccctggaaat tccccatggg aagggaaaaa 240
gatngganaa aagggancat ttattgccaa gggaagantg ggcatctcgt ggtccccttg 300
ggttgaaacc caanattcca ttaagggaaa gaacgggtgc caagttgttg aagggtgggg 360
acccttggga cccttgggaa taaaaaatgg gggtggttta aaccaaaagt aatttgtttg 420
aagtaagggt tgggtgggga agggaaggca ccgactaaga tgcaaggggg tctaagcttg 480
aagttggaca aagaagctaa ccaccagggt tgttgggacc aagggacagg ggggggaccc 540
tttaaagccg aaaagaacac cctgcccaag atggtggtct ttggttccct ttgacctggt 600
gggagaaggg ccccttggt gggggtggg 629

<210> 167
<211> 276
<212> DNA
<213> Homo sapiens

<400> 167
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agcaaagtct tctagattaa gcggtcgctc caataaagtt tcctgattct gtccagaaat 120
cctcaactcc gacaataaga agtgggttga ggggcagttt gaatacataa tcaaaaagca 180
tataattgaa gattgaactt gagctatagc ttcatgtatt gtctctgcgt tgttctattt 240
taatagttgc atatggagac aataaagcta catgac 276

<210> 168
<211> 299
<212> DNA
<213> Homo sapiens

<400> 168
agacgtctgg ggagcctacc tgcattaagt ccanatactg gagagaaatt caagaacctt 60
ggaaagctta ccccaacctt tcttaaccat tggcctanta accnatggan caccccttaa 120
ggaangtggg gcaggaagta acccccggan ggggaaagaa acccctgggn taaccttgga 180
aatggactan tattggaaaa caacanggtt ggcctttana taaccccttc ggantcaact 240
tcaacttaac nggaaacttc ttntaaataa aaaggtanta attttttaa agcccaatt 299

<210> 169
<211> 540
<212> DNA

<213> Homo sapiens

<400> 169
atttctgtga atagaccaga agcccgacct ttacagtgtg tttggggtgc agaaaacctt 60
ggctgacata ctcaaggctg aaatgcagtc agcggaaatg gaaacacttc aactctgccc 120
ctgtggcaag aatggcttcc cttcagacaa tctggccaga ttctttatgg acccaatggg 180
agaaattgga tgcttgtata tacctctcag catctttgaa ggggcactga aacttcaatc 240
aaattgggga aagggagccc tgaactttag acctgtttta aatgtgcaga gtggcaactg 300
gcacaaggaa cacttttccat ctgtaagaaa gaatacaaag aacttggaac aagaaaaaag 360
tagatatctc atcagtcaat ggtgctgtat aggcatgcac aaagatggag atgtgagcac 420
cgacaagatg gctggcatct ataaggcagg aagagatacc tcaccagaac cccataatgc 480
tggcctctga cagtaaaatt ctanctgttg nactatgaga aaataaaatt ctgtggttaa 540

<210> 170
<211> 381
<212> DNA
<213> Homo sapiens

<400> 170
ctgaatgaag acaaatctta gccctctgag actgatggtc tcagaaagta gtcttcagat 60
taccagcttc agaatcagct gatgggttca ctaaaatgca gattcccagg cccagtgagg 120
actgaataaa tcttagtttc ccaggcttta caggaaccat ggtgctcagc ttctaaggag 180
gcctcaggaa acttacaatc atggtggaag atgaagacgg agcaggacac agagttcacc 240
ctctctggag aatgtagcca ccaggcacca tcttggaagt gaagactgga ccctcatcag 300
acaacaaacc tgccagtgcc ttgaccttgg acttcacttc ccagcttcca gactgtgaga 360
aaataaactt ctgttcttta t 381

<210> 171
<211> 334
<212> DNA
<213> Homo sapiens

<400> 171
ataatgacga ctgcaaaatg gcaggataag gaccgtccaa aaagcctcat tgatgaaagc 60
aatgagaacg ctggcaaaaa tgatcagaat cggctttttc agacctctgg aaattaacca 120
aagatttgca gtgaggaatg aaatttcagt gaaaagcaat atcctagcag ccactggggt 180
ggagaactga agccgagctc ccccaaagcc tcttcccgga gaactgtcat tatctgagct 240
gcctctctgt tccgtggaag actctacttg caagactatc tttgcctgat tgactcggag 300
cttaacccgt aggaacagcc caggggcatt tgtt 334

<210> 172
<211> 351
<212> DNA
<213> Homo sapiens

<400> 172
aacagttcta gatctccatc gttataaaag agtattaccg tgttggtgta ccacaatttc 60
tcaagaaaaa cattagctaa gcccaagctg gattttgatg gataacatgc tgatgttgta 120
acaaggctgg agcgtggcac atctcacaca tgcaggtgaa cacccaatta ccacgcctat 180
gaactacaaa atcatctaag cagattttaa attagccagt tgtttcccta ggatcctcca 240
aaggtgatca atacagtttg ttttttttctt ggtggaggga tctcatgatg aactaatgaa 300
tcttaacatg aattgtaagc aaataaataa aatggtatgg tttaagccat t 351

<210> 173
<211> 376
<212> DNA
<213> Homo sapiens

<400> 173
gcatacctca agatcagttg aattggagca cagctggatg gaggcctcag gttaattaac 60
ttccttgag agcatccaga aaattagcaa ggacatgaga aaccattcac tcaggacgac 120
caatcagcca ggacactccg aaacctatta aatcagattt ttaatcttct aagcctgtag 180

acaactgtgt gacatcagcc acatcctcaa atcttaaggg aaacacgaat acaagaatac 240
atgtgtgcaa ggaatcatgc ataaaaggat tgtgccttca gatcaagtcc aactgttttt 300
atttgtcatc aaatgtgaac ggagatatgg gtactagtcc caggaatgcc ataaactagc 360
agtgaatcac ttcttg 376

<210> 174
<211> 513
<212> DNA
<213> Homo sapiens

<400> 174
atatgtattc tgcaatcatg accaaacaga aggactaaat ctggatcaga atctgaaatg 60
taaaaaggct acttgtcaac cacgccattg ttttccgttg gagctagcag agcagcctcg 120
gctgcacatt cctgggacgt gaataatatc ggttgtgatt acacttcagt atctcatcca 180
ttaccagccc tgtgaacact gaatataacc taattaggaa atgcgaaggg ccctttgcta 240
gggatgagtg ctggggcagc agaggtccac atgccttccc gacacaggga ttcaccgggt 300
ttcagacaca ggtttggatc ctgcagggct caaggacaga ctttactggt ctagtccaca 360
ttccttgtat aatcaccagt aagctgagaa tgtgacacct tggattccat cctatgttac 420
actcctcttt aaatgcattg caaaggagat atgccaggac ttgataagtc aagtcaattt 480
caaataggta ttaaagtatt aaatgaagtg att 513

<210> 175
<211> 432
<212> DNA
<213> Homo sapiens

<400> 175
gtatgttgca ttgtacaaga tgaagttaga gtgtgaagca tggaacaaag tgcttattga 60
gccagaaaat actgcccaac cagctctcaa ggcaaagaga gggtgtacga gaagctaatc 120
ttcaaatgag aggtggagac ccagctggca gctagcatgg tgcggcgtgt tggaggcaag 180
aagcagaatc tcagactggc aagatgcaag ggcaggcagc ccacccacag ggaaggcgtc 240
gccaatcttg agcaactcta gaagagaaac ctgaacacat cagaactcaa actaactgat 300
aatgaactgg ttttcattac ttcctgagtg atcaggaggt agaattgtct cttacaaccc 360
aatgtatacc attctcagtt gtctatttaa ggatttctta gtgagctcca tggtaaaata 420
tatctacttc tt 432

<210> 176
<211> 387
<212> DNA
<213> Homo sapiens

<400> 176
aggggcagac ccaggtggga gtactgcagg ccacgcccct cgaagacagc atccacgtgg 60
tcttccgata ctagcaaggt gtgcttggca gccggtgcct caaggattgt tctggaagga 120
tgacatcact caaggtgtga ggacccagca gacagagcac acgccctggc tccatgcccc 180
agaggcccat ctgaggagcg gacaggcagc ctttcccacc agagtcacca gggtgaggac 240
gtctttgagc cattcctac tctgagtcac aacctcgtag ctgattaagg ccacatggga 300
agcttcccat tcctcatact tcccctgatg ctctcaggaa ggacaatttc gggctgaacc 360
aaatctggat tattaaagtc aattttc 387

<210> 177
<211> 420
<212> DNA
<213> Homo sapiens

<400> 177
gttgctacaa taattccagc tgtgtatacc tcctgggatc ataatagaaa tgaaccctctg 60
aagcatctta ctgaagaagg cccctacgtt gactgtccag ctgactgtct ctacccgact 120
gctgtcccac acaatatggg ccaggcgatg gtattgcctt tgcaaactaa atgaagttcc 180
tcaaagtgaa gctggtggcg acttcagagt taacttttca aatggccggg cttatataga 240
ataacctttg taaaagtaaa ctatgatcat ataataagat acatgtgcat ttggaacgcc 300
actgcttttg gaacctgtct cagtttttat catcatacaa ggttaattgt ctaatgtcaa 360

ttagatttta tcacaagtgc atttgggtcc taatctggaa caataaaagt ctattaaacg 420

<210> 178
<211> 421
<212> DNA
<213> Homo sapiens

<400> 178
ggcatcttga agcagaccag ccacgttgca agtgcttgga ggcacggatg actggtggct 60
gctgttctgg gagacagaat cctatagcat ccccagtcct gcagcacaca ggtgggacaa 120
ttccagcttg atgtctcagc cagcgggttc ccacgtcctc cccgcctctc ccaggcagaa 180
gacagagtga cccaggtaac caggaaaaca aggccataaa aaaggaactc ctactaatga 240
aacctcctag attccaagga ggaaaacgta gctctcagac caagtccgtt ttcgcccttg 300
catctgaaag ggagtccggg gaattgctaa ttttgaactt tctatacacc cttcctgcct 360
ctggatgtgg ccgcctgact cgaattcctt tgcacaataa aatgaggggg aaaaaaatca 420
c 421

<210> 179
<211> 115
<212> DNA
<213> Homo sapiens

<400> 179
aatacgttcc agaggacaag gactgtgttg ttcatcacag tattccagaa cttaaaagga 60
actggcacat aattggagct tactaatatt cgtcaaaaaa atgaacaaat gaggc 115

<210> 180
<211> 449
<212> DNA
<213> Homo sapiens

<400> 180
ataagagtga gcatttttgg aaatgtgatc aactgacgca aaatggcagc aacactggaa 60
ggaagaatca ggaggatatc ttagaagata accacagaat ctttgcaaga gacacagaag 120
actaccttac acctggtttc cacaggagaa atggctcaaa atatgttatt agttgaacag 180
taggaaaaat gtctatggtc tcttcagcac catctgtatg tagtctctga gtctccagtt 240
tctcatctat gaaactggga taataatatg caatgagagt tattctgaag atcaaataag 300
atagcatgtg aaagcagttc tagattccag acataagagt aagattaaaa gaaatgttgt 360
tctcaatttt cttgtgtcat tgctgctgcc atctagactt aaacaaatgt tactgtaaga 420
gccaagtaat aaactaacac atctaatcg 449

<210> 181
<211> 506
<212> DNA
<213> Homo sapiens

<400> 181
gtgattttag aggaataaac acccttagcc gtcagccaac attttacaaa tgaaggccag 60
caagggaaag gagctcactg aaggcccatg ctcattaatg aggaagcaaa aacaacagca 120
cacagcctct gttcccaggg ccacgctcct cgatttctaa gcgctgttcc agtccacaca 180
ggacaagaca tccttttttc ttctagaaca acagctcagc cccacctgaa agaaagagtt 240
cattgatact ttttcaaagg cttcacaact cagctttttt ggagacttca gcaaaataag 300
tcattatctg gccaacttta agaatgaggn ttgctaaatg tatcagcatt ctgaggntat 360
cagaagactc tgcacacttg catatctcac aaataccgnc aataaataca tagnttcatt 420
tcctcattgg ttcacaaaaa aaaaaagggc ggccggggcc nttnanctttg gacttaanaa 480
gggtggaatt tnttaaaagg gggggg 506

<210> 182
<211> 510
<212> DNA
<213> Homo sapiens

<400> 182
gccccagcgg atggaactca taaataaaga gtgagaaatg caanttatgc cagangttag 60
aaagccaggc tccttgccac agcaagaagg ggatagctgc agcccacgga gaaggagaac 120
cagtaaagtt agcaaaagca ggcagaagaa gtttctaaag caacatactc tgcaaagcag 180
tctgggccat gtactgtagg agcaagttgc cagcagcccc cgggagcatg aatggatata 240
gcaactgttg ttgaaaaaga acaatcctga tcaacccaca tcaaaggcta atagacctca 300
tttaagaaga cagggaaatg taaatctgtg agatacttca ggatcatttc tatcaaaaag 360
cgtttcatat aataaaggaa taaagcctca gttatctgga agggtcnnnn nnnnnnnnnn 420
nnnnnnnnnn nnnnnnnngg gggccggggg gggcccttttt ttttngtttt aacccggnnt 480
tntttttttt aaaggggggg ggccccccca 510

<210> 183
<211> 379
<212> DNA
<213> Homo sapiens

<400> 183
gctcggtgac taggaagagt ggctgaaagg ccccacctct gactcctccc tgcttctgat 60
agcctgagtc ctgggggaca gagggaagcg cctctgggtt cccctctccg tgtgaggcag 120
acagcctccg cccaggctct gaggggccct aattctttcct aacagacagc agtttggagc 180
ttctcccaga gtgacccagg agccagccca ggagtggtct agaatagaca aaggaccgtt 240
agtatcccga tgtgaatttt agaatgtgta tatttcatac ataaaaatag aaatgtatat 300
gaatgtaata tagattatat atttattatg tatgtaaaaa cagtatgtgc acatgataaa 360
tgagcatatc tacgtctct 379

<210> 184
<211> 317
<212> DNA
<213> Homo sapiens

<400> 184
gacccacctg ccatgctgtg aggacaccca ggccacatag agagagtgag gccacatgta 60
ggtgttacag ccagaagccc cactgaaaac caaacctgca accagcatca actgccaaac 120
atgtactgaa gaggctgaga tgattccagc acttgtggat gactgcaacc acatgagaga 180
cccagagcaa gagctaccta gctgagccca gttactccca gaatcatgag agaactatgt 240
aattgattgn tattactata taagccactn ngtttncntn tgatatgtta tgcagcagta 300
gacagctgga acaggag 317

<210> 185
<211> 378
<212> DNA
<213> Homo sapiens

<400> 185
gtgcagtgaa caaccacgac aggcttcaca tcatcctacc tggtcagaag ttgccaccat 60
taggacaatt aattaaattc aacagtaaag atgctgccat agttaatgaa tcatgttttc 120
cctggagctt tccacctatt caaaggacaa gtttcagagc ttggatgagg agcaactatc 180
ttatgaacac agagacattt gtcagtttta aaggtcaaat tagatttttg ctcaggttcc 240
caccaaaatg atagacttga aaatcaggat ttatcaaact atgttctaaa ttatttcaac 300
atatcgagtg tattagtctg ttttcatgct gctgataaag acatacccga gactgggaat 360
aaaaggagga ttaatttg 378

<210> 186
<211> 688
<212> DNA
<213> Homo sapiens

<400> 186
ggntcccctc tgttgnccan ggctggnagg cnnggggcgg gaaccttnnn taactggaac 60
cctgggcntc nggggnnnaa nnctaatcng cggtgncntc gggcctggcc aaaggaagcn 120
ggggaattaa caggtccggc gccgtcaccc aangccccgg ctaaaattat tttggcaatt 180
ttttttggta agaagaacgg gggggttttt ngcgcattgg tttggcccaa gggcttgggn 240

cctacaaaaa antccctggg ccctcaaagg ccgaatccca acccccggct ttcgaaccct 300
aacccaaaag gtggcttggg ggaatttaac caagggccgg nggaagcccc acccggccgc 360
cccggggccc aagcctggga ataagtnnct ttaagtgaat caaanatgaa cctggnnggg 420
gcctgggaaa ccctcaaggg gggaaggggg gccctnnacc cttctnnggg naaaacnnat 480
cctggggatc ctggacaagg gggncctttg gcttccattc accccaaggc ctcaaaagtg 540
gaaaggggng caatgaancc tccgggctca acctggcccg ccttggaccc tnccctggaa 600
gcctcnaaaa gggaancctc cccancctca agccctcaaa ggaanaannc taagggacnt 660
gganggcnaa gganaccaat tgcccccc 688

<210> 187
<211> 404
<212> DNA
<213> Homo sapiens

<400> 187
gtgactgcct aatgttaaca aagatctgta ggaatgatgg gaaggggcac tggtacttnt 60
ctctttccta atccttcaag tcatacctga agatccgcag ttttttctgga gacaggtgaa 120
gtccagcccc tgaaagacgc agacagtgca gagagaagag cctacgtttt tatatttttg 180
tcaaggtgat gtctcaagca aaatgaagtg gtttgtggct gaaacaacct ccacgggaaa 240
gaaaactgga gtgttcgttc atccatcaaa gaacaaacgc caacgtctga gccaacgacc 300
ccagctcccc cagacaaagc agtgaacaga ttaaaggatg ggaggaagga tacaatcaaa 360
atcgggtggt gatggctggc agataaaaat atggaacgct tcac 404

<210> 188
<211> 552
<212> DNA
<213> Homo sapiens

<400> 188
gcagaaggcc ccanaaggnc cgcaagaact ccccanaaag gccngcaatn nntccgncaa 60
gaagggcccg gcngaacntc ccgcaagaag ggcccgcaag aactcccgca gaaagtccgc 120
cacacangca aagggaaaga tgcctcccgc gtccaagccc ggcttganat gagcaggccc 180
gangagccaa tggcgcaaaa gaagngnccc ggtntcccgg atcgggnant cctcataact 240
ttnccttten ttctggacca aggtaaagcc cacaagagnt atgggaaaaa agngcttggg 300
gggaaaggaa ancnggtggc cggaagttcc ttcttcccaa ccaagggncc cactnaattt 360
atnggggagga aacccaaaaa ggcgtttttt ccttaaaaaa cctggaccgg gggaccaaaa 420
tccgaannngn aacctggacc cacttgcagn accattggga cctttcccen taaacctttc 480
aaaatctngg tgggaagaag aagggccctc aagaaggtcn ntccactccg cctattntca 540
atttatcaag gg 552

<210> 189
<211> 317
<212> DNA
<213> Homo sapiens

<400> 189
acttgcaact tatgtttccc ttttaatcac aaagctgaag aatagacaac tatacgacct 60
atcatgaagc aggaagaaaa aaaatcatcg acatttttga ccatgcaaat gagcattttt 120
tttctgcaga ataaactaag gctaacaaaa aagacaaaaa caactgatca ttcgtatgaa 180
aacctaatta tttggtggat ttttcaaaag gtggtcagct aattatgtgg tatcatctgg 240
accaatgttt tctaggcaag cctagatggt caacttttga gagagtttat aataaagttt 300
gatttgttta tgcatac 317

<210> 190
<211> 370
<212> DNA
<213> Homo sapiens

<400> 190
tgctgctttt agaccagtcg cacaccaggc cgaagaggtg agagggtgag gtgtttccca 60
caagaacatc cacatcctca ggatggatgg aggagcaagg acgagaacca ccaacccccg 120
agacagtttc tggctccttc cttccaagaa gccctacaca tgatatccac gttgaagccc 180

tcatgcaaca agctactcat tcctcttctc aaaggaagtg ctgagtgtct ggcaagttgg 240
aaagaatgag ggattcttct actgggttac ctggtcagct ccgaggagag ttaaaccagg 300
aaaagtagtt caggctggta tacctccctg tttgtccttg agggcaactt aaaagcacta 360
tttacacaag 370

<210> 191
<211> 427
<212> DNA
<213> Homo sapiens

<400> 191
catgccatgt ggacgtgacg cctggagata tcgcacccac cttataatca ggaggaagaa 60
tgccacgtgt ggaggatggt gccacaggaa tctggaagag ctcgatcctg gacgacttgc 120
tcaagcagct gcacattcct cctgccacct acttctggat attgtgttag gaaactggca 180
tgagcataca catccattca gaggaggtga aagtggagtg actgatgcta gaatccccac 240
cttctgagtc aacggtccag agaacaaggc caaaacagcc acaaatactt ttcaggcttc 300
aggatcaaat tttttattct tgaatgatcc aaacacttta agaaaaataa agtttctaga 360
ggaaatcaac aaaagtgggn nnannnnann nnnaannnan aaaannnnnn nngggggggcg 420
gggggc 427

<210> 192
<211> 453
<212> DNA
<213> Homo sapiens

<400> 192
ctttggtgtc tgcacagtcc cacacgagcc aagcccggct tgcagggtca agctgtcttt 60
tcatagtggg aaaaagctga tgaaaatcct tcacacagag gtgttaagag cttaatgatg 120
aacactcccg acctgagtta taatttcaca agaatttgaa ctttattttt ctgcggagag 180
tcacgtgatt tgtcctgcgt gccaataaaa ctactgatgc cagctggcct gaagaactcc 240
atgaagatct gactgactaa agaatgcagt ttccaatcct ggtgatttca tcccccttat 300
cccaagcagt caataacttc tactttccag cctcttgtcc tccacgatcc ccttaaagac 360
tctagcccaa aactccccag ggagatggat tcgaggattc ctctgttcgc tcactcagcc 420
actctgcaat cattaaactc ttttctctgc tgc 453

<210> 193
<211> 453
<212> DNA
<213> Homo sapiens

<400> 193
tctgtgtcat gctgccttct gtagcaacaa cggctgntcc ctgnttntgt gccacatgcc 60
aaactattca acatntgcac atactctcct agtcactctt aagggtgttt cataatgaag 120
aaactgaggc cgtgaggact gaggggcaat gctgcagcaa tgtcaagttc attcggtgga 180
ccacgtgcct tccatctcca aagacacagt ctgtgctcct taaatacctc ctgacaaact 240
caatgtgcag aggcaagata gagcaagttt ctgctgcaaa ctcaccacca gtagtggatt 300
ctaagcccan ctncctgcca atgattcttt gcagggncac agcttctgtg cctgttcacc 360
tagggctggn tnaccacagg ganggancnt gattggggaa aagcattggc ngtnncagaa 420
tggaaaangg gacctcaaaa ttttgtctta ggg 453

<210> 194
<211> 473
<212> DNA
<213> Homo sapiens

<400> 194
gcttttggca tctccattca ttccggaaca gccagtcagc cctctctgct gtgtcccaga 60
gcaccaggaa gtgagtaaca gtcctagagt gagacatgga ggatacagcc aagtatcaga 120
ggagtgctgg ctcgctgctg cttctacacg tcaccgtact gggggaatcc tatgtgaagc 180
cgccccatgt cctgtctgcc tggatactca ccatgcagat agctctctgc attcagcagg 240
gtctggctta ggccctctcc tgggggccgg agacccctct gttcttctcc agaccctgca 300
gaattctgga gaggagagga aggtggaaca cacactttct tnctgctttt ctanggtgnt 360

ggggcatctc tcttcttctt ttaactacga acttcacagn ccaaccactt tctcttttt 420
acaagcccct tggggtcctt caagaaccaa agtaaaaaaa agctttaaaa atg 473

<210> 195
<211> 127
<212> DNA
<213> Homo sapiens

<400> 195
ccattgacct ggatggacct aggacacaca ctaaaggaca catctggatt caccaaggag 60
ctttttatat ctcacaaaat agcatgttgc taataagaag aataaaatga aaccaaggta 120
caaaatg 127

<210> 196
<211> 311
<212> DNA
<213> Homo sapiens

<400> 196
agaaagaacc ttcaggnntn gggaggtggg nctttтcntn cntnaaaacn atgatncctt 60
gggtganccg nnnggattgn cccacaancc ccgatggaaa cattcaanag gngaatgcct 120
tgctcanaac cccctggcca ggcttaggag ggaaaaanta tgctttccaa ctntggcaag 180
aaattgctgc atccanaggc tgcagaagcc ccgaggagca tgaacatgct ttggaagaat 240
angcgctgcc ttgagtgaca tcctgaacca gacccttaca cacacanctt tcattggtgg 300
cttttggggt t 311

<210> 197
<211> 497
<212> DNA
<213> Homo sapiens

<400> 197
caactgtgga agtcaaggcc agaaatcact cactatatca tctgatattc ctctgatcgt 60
tatacctatt ctcagtgtta aggaaatgag accagttgaa acgtccacat taaaataaga 120
agaaggagag aaggtttтct aattgcagtt aatgtcatcg ttaaataaag aatgccataa 180
aggaacgaga tcagcagtga ccttctgcac agtttccaaa gcctcgccaa cctacctccg 240
tgtcctggtc tgacttatgg cagaaacaga agttcaaaga cctggctgat atgctccgtt 300
aaaaaccctt ccacaacgca gttaacattt tctgntttct gactttcttt ttctaaagag 360
atgcttaaag caaaaaangg ttcctgcccc aaaaatgaca ttaatatttc gtaaatcaag 420
aactaagata atggtttngg ctgctacaga gaccgttacc cttatgcggt tatctnaaag 480
cttttcgatt aaaacac 497

<210> 198
<211> 350
<212> DNA
<213> Homo sapiens

<400> 198
atctgaagag aagagaaacg tgagggaaga acaggcggtg gcagccggaa gagagtgggt 60
ggaacagtcc ctgcaactct tcagagaaaa gaaaggggcg ctggcccagg cccaagaagt 120
gtccctgggg gccgatgtcg gcaggaatcc ccgcatctcc acatgcggaa ctgagagaag 180
tgcctggcag attcaatcat acagtgactc aaatgtcaca gcatgactat agagaaagaa 240
taatagtgga agcatcccgg ccaattttca acagaagggc tcaggataag gaagcttaag 300
aaaattgccg aagagaatga taatgacaat aataaaaaca aatagcttcc 350

<210> 199
<211> 275
<212> DNA
<213> Homo sapiens

<400> 199
caggtgaata aggtgggatt tgaaatcagc atggcagtgt ccagtggaag aagggagctg 60

aagtttcttg aggatgaata taaagctggg ggagttatca ttgagcctaa ctctctggtt 120
tggaacccat aaaccctaat caatatacct cccaagttta caatagaggt gagtatattc 180
taccttactc catttccatc ccaacttccc cactttgtaa actttcagaa ctgacttatg 240
gaggtttata acagccagat atcaaaccca tagac 275

<210> 200
<211> 354
<212> DNA
<213> Homo sapiens

<400> 200
agaaagagga aaggaccagg agtggcgacc ggcaaaccac agcttgtgtg ggaaggaaat 60
ttgacatgtg atgcaagcgg accgtttgtg taaactgctg ggagattaac aacaactgtg 120
agtggaattg ctgagtcatg tggcaaacta ccagttctgt tgaacctcag ggccatcatt 180
ctgttcatgt cagctcgttg tagaaccaca tcgatgaaga ccaagatggt aaagatgaaa 240
aattgtagct aacatttact gcacatttac tacaagccaa gcattgcact atgaagttta 300
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<210> 201
<211> 310
<212> DNA
<213> Homo sapiens

<400> 201
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caagtaatta ctgcaaatcc tgccctggg tcaaaacaac cttgatgaca tattccttct 180
gaagcacata tactctttcc ctaggtatat aagccttggg tctgggggct aacggtgcag 240
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tttcattctg 310

<210> 202
<211> 446
<212> DNA
<213> Homo sapiens

<400> 202
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atcttcaggg gaaacgacac gagtaccctt tgcttttcct caacgaactt ccccttctact 120
tagggtttta gggcatttgt acaaatgatt tgttccttgg gtctgaatct tggggatgtt 180
tatcattttc gttgctttca gaaaatagtc tgcatttcct tctattacct ggaccatttt 240
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gacgaattga gctcttcctt ctctcgaaca cgggggcacc tctacccgct acagacttga 360
agatttact cacttccttt catcccctcg ctcgggtttg gagggtaggg gcatgaagtg 420
gntgaatcta aactggcaga aaaccc 446

<210> 203
<211> 88
<212> DNA
<213> Homo sapiens

<400> 203
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tttgctgaag aggagaagga aaaaaaaa 88

<210> 204
<211> 211
<212> DNA
<213> Homo sapiens

<400> 204
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gaggnggctt gagtangatt tgctgccagc taaagcgtga gatgctattg catgtgcaag 120
gcaaggcttt cttcancggc atcatcttnc aaaatagccc agngagcatg cctttctcct 180
gaaaaataaa aaatagttgg tgtttactgc g 211

<210> 205
<211> 245
<212> DNA
<213> Homo sapiens

<400> 205
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caaagagaag gggacactgc accatggagg tgacacaggc cagtggccac ggtgctggac 120
ctggggctga gaggacccac atgtatatcc tggccgattt aggtatctta gactttctgt 180
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cattg 245

<210> 206
<211> 325
<212> DNA
<213> Homo sapiens

<400> 206
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gctcattctc tccacttggg aaggaggcta caacttacag tgtcaagatc ttaccagcgc 120
aggggaagct gacatccgga ggaccaactg aataaaccac agcacatcca cgtagcggat 180
gcctctacca agtggagtga ggaagagctc tataccgcta cagaattgtn tctgggatat 240
agttacatga acaaaagcaa cttgcagacc gtgtttatag gatagcaccc tttgtgcaat 300
aaatgatatg aatgcaaaaa aaaaa 325

<210> 207
<211> 232
<212> DNA
<213> Homo sapiens

<400> 207
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aatcaaggga taatggcatt tgagggttcc tcaatgaccg cccagccaca tcacaccgga 120
gtggagcccc aacctgagag gctcttaccc agagcttcca gtcggcattt cagtggatca 180
cttttaaaaa taaatggtga tggggtgatg gaaatgctac ccccaaaata cg 232

<210> 208
<211> 159
<212> DNA
<213> Homo sapiens

<400> 208
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aggatgatgg aagaacaaga gagaagcagg ctggttcttt gacattggac agccagagtc 120
ccagccctgg atggcctgtt ccagacatct tgtcaagtg 159

<210> 209
<211> 329
<212> DNA
<213> Homo sapiens

<400> 209
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acatgcagga gaaattgcac agatagaaga actgaattaa caatctccaa gactgctgag 180
tggttttgat ctgccttgct tacttttttca gccgctttat atgctgaaat gtttccagtg 240
caaccagaag tttcaagtgt aaaattctgt ctttcctctt ctgttatttt aagcttttaa 300
gacaccatac ataanagcaa ataaatgac 329

<210> 210
<211> 133
<212> DNA
<213> Homo sapiens

<400> 210
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cagtagaaga aca 133

<210> 211
<211> 270
<212> DNA
<213> Homo sapiens

<400> 211
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actcatggga gaatgcactt tccatatttct aatgacttca tccccttac cctgaccaaa 120
cgataacccc aattttctaa ccccttgccc tctccaatcc cctgaaagat ccttgcccag 180
aacccctcaa tgaaatgaat ttgagtctcg agaattcctc ctgtttcctc attcagtcat 240
cttgcaatta ttaaacaact tgtctgctgc 270

<210> 212
<211> 355
<212> DNA
<213> Homo sapiens

<400> 212
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gctggccttg gtgggacttg ctcagggact cactgctggc cttggggagn acanaactca 180
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cccaccccag gaggatcacc catatncaac nccnggagca gcntcagcca cnctnnaaac 300
aaggggaaa cgccaagccc attacattag gacttttccc tgccatcact gggct 355

<210> 213
<211> 397
<212> DNA
<213> Homo sapiens

<400> 213
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catacatcca cagccccagt cggctgtatc catgaagagc tgaatggaac aggatgactg 120
gcagcccacg ccaagggcca agagatgtga aggtagaagc aagaagttag aatgacctga 180
ggaagaggtc acaagcccag gaatgccagc agccactaaa agctgaaaaa aggcaaggaa 240
atgagttttc ctctgaagct gccagaagga acaagcccag ccaatgcctt gaccctagcc 300
cagtaaaatt gattttgaac ttccaaaaaa aaaaaggncn gngnggccan ttnagntngg 360
acttaaccag gnngaacttg ttnaaaaggg ggggggc 397

<210> 214
<211> 141
<212> DNA
<213> Homo sapiens

<400> 214
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tagtctaagc tcccaaagaa ctggatgcta atccctgtcc tgatactaac tcaccctggg 120
acattaaaca ggtcaaaaaa c 141

<210> 215
<211> 96
<212> DNA

<213> Homo sapiens

<400> 215
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gctatactat acatgtaatt aaaagttaat tatctt 96

<210> 216
<211> 305
<212> DNA
<213> Homo sapiens

<400> 216
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aggtttatag aattcctaag aactcaggaa agacatcagc agagagcaat gatcgtcata 120
gccagctcca cacagaatgc acccacccag ctacttgtcg aattacaacc tgatgatgga 180
tccaccagaa actaagaatg gaaaggttat aaagaaatca cagcattcat cttctggaag 240
aaaaagacta tttcttagaa agtaaaataa atgaataaaa gcacttaata aggagcataa 300
cgcgc 305

<210> 217
<211> 427
<212> DNA
<213> Homo sapiens

<400> 217
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ttcaccc 427

<210> 218
<211> 438
<212> DNA
<213> Homo sapiens

<400> 218
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ccagaattac ctcagtatca tagcgtaggt gctttggaga aaactgactc ctcctagcaa 120
taagtcttca gttgctttaa gctttaagca cattctttca gtcctctgat cactgtcatt 180
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atgctgagac agaagtacag gctctcactt tctctgcagt tggcagagag ggaatgtggg 300
ctcgattgct tctggcaaac attgtgcaag tcatgttggg aaaggggact tgaaatgaag 360
cgaagattcc agaaaacaga acaaaccaaa agaaatggtg accactataa ctggcaactg 420
tggagcctgc cctatctt 438

<210> 219
<211> 424
<212> DNA
<213> Homo sapiens

<400> 219
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aagatattca tggtatttgg aaactcttat aagcaagaag tccgaaaagt tcaagatact 120
tctgtagaat ggtttaattt aaaaagtggc tgctatcctg gatggggtta agaagctgct 180
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ttaccttctc cataaagctg ccagaaattg ctcctgccga gagtaattta cctcttacac 360
accactgtta tttcactgtg tgggactgna ttcccaanta aattgagaat gtctaataga 420

tttt 424

<210> 220
<211> 318
<212> DNA
<213> Homo sapiens

<400> 220
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tcaccccgca tgagacgtct ggcaaaataa gaaggctctc gcaaaaccta acaaccaaat 120
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gctggaactg gggtttaaaa aaagaaaatg tttacaaagt ataacaagat gtttgatggg 240
tggaaaaatg tatccacgag ttacatcccc ccgtttcctt gcaaagcccc gctggtcttc 300
ctctcctttt cttctgcc 318

<210> 221
<211> 227
<212> DNA
<213> Homo sapiens

<400> 221
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ctgaaactat ccatcagctc tcctggttct caggctcctg gattcaagct ggaagtacac 120
atcaggtctc ctgggtcctc agcttgatga ctcgagatct tgggaattct cggcctctat 180
aactgtgtgc cccaattccc tataataaat ctttgtcttt ctctccc 227

<210> 222
<211> 462
<212> DNA
<213> Homo sapiens

<400> 222
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tgaagaaaat gctgctctgg ggacactaat tgaactttca tctagcaggt cctgtgccct 120
acctactcaa gaacaagttc tgtttgatga agaagttaca cagctgccaa gttccctcat 180
tctactacct atctaccccc aaattcagga atgtctccat atgttgacta tgcngacttt 240
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agcttactaa actataaatt gtcaactgta ttacatgata aagcagatgt gtccatacag 420
taactctttt gctaataaat gaggnctaaa ttccaaaaat ag 462

<210> 223
<211> 465
<212> DNA
<213> Homo sapiens

<400> 223
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tgctattgaa gcaccttaat gacataaaga agaagaaacc aatgaacatt gttatatatt 120
tcattttaaa ctgatgtaga cattttgagg aaatctgcat tttgaaccag gttaactgtg 180
gaatgcccctt ggccaagagg aggggtccat ttgatgattg gatggcctta gaatttattt 240
ttggttaata gtgccacaca gctaaatcca agagagtgtc ttagaaaata aactctggaa 300
acatatttga gaaactaata agaatgatta actgtagagg gaagtgtcag gcctctgagc 360
ccaagccaag ccatcgcatc ccctgtgacc tgcactatat gcccggatgg nctgaactta 420
ctnaagaatn cccaaaagaa agnggatttt tgcccttgcc ccccc 465

<210> 224
<211> 184
<212> DNA
<213> Homo sapiens

<400> 224

accattagaa tgtgacctct gtgaagacaa cagaaatgga ggaggcgatc catgggcatc 60
ttctgaagct gttttggtta actttgattt ggaagtcctg gttccaggtt ctcctgtttc 120
ctgggaccag ctccagaagt tcattatttt cataaataat aaatgaatgc atactaggga 180
ctgg 184

<210> 225
<211> 124
<212> DNA
<213> Homo sapiens

<400> 225
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tngccntttt accctggaag aaatactcat aagccacctt tgttatttac ccccaatctt 120
caca 124

<210> 226
<211> 374
<212> DNA
<213> Homo sapiens

<400> 226
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atggcggtgc cacagatgga gaaactgaca ctcagacagg ccaactgatc tgcccacatc 120
aacgagctaa aaaaatggca aggccaggat ttggccctag gcctgcttaa ctctgaagac 180
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taccccactt ttgctgggtt gaaaagggtg aaaggggtac cccactgctt gttgtacccc 360
accccaaatt ttgc 374

<210> 227
<211> 318
<212> DNA
<213> Homo sapiens

<400> 227
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cacacttgag tgaatagcga cagctcgccc cttctgcgct ttgacgctgc tgtctctact 120
ggccacttgg tctaccagtc agttgtgccc tgtatgtacc cagccatggc tgggaagact 180
cacaaccaca agattgccta tcagtaggaa atacaggaaa ttacaggatg ggtatatgag 240
acatatgtgg tggatataaa gctcaatagt agtgatacaa gtgtcatatt cagaaaataa 300
tataaacttt cttgctat 318

<210> 228
<211> 502
<212> DNA
<213> Homo sapiens

<400> 228
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ggccagcagg ggaggaggcc cagtcctgaa agctgaacaa acgcccggca cacaggcctg 180
cctgcgccct cgtagtctct ctggacttat gaataaaaga tggaggtttt gtctctgttg 240
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aaaaatgacc aatattaact ttacatgtct tggcccttaa atctggagtg gggtaaaatg 360
aaagaaacaa aagccatgta attangnaga agataataat tcaaggtaaa ctaatgaact 420
gnctgnaccg actttattaa aanatggngg gacatgccat cccnaactaa aagnttaaac 480
ctgacttgga ggaaccttgg gc 502

<210> 229
<211> 228
<212> DNA
<213> Homo sapiens

<400> 229
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actgaaattg gagtgatgca gncacanncc aaggaatgcc tggagccacc aaaagntggn 120
agangcanga natagactct cttctatagc ctgtggagct ctggtaatac cttgnttttg 180
gatttctgcc ctccagaacc atgacagaat aaagttctgt cttaagcc 228

<210> 230
<211> 395
<212> DNA
<213> Homo sapiens

<400> 230
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acttgctttg ttcgaactgg ctgcatgact tgctttgttc aaccaaatgc tgcagaagtg 120
acggtgcaac acttccaaac ttaagaggct ttgcatgctt ccatccctgc tcttgatttt 180
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aacccaaata agccaagcct gacccagctc aacagaacta tcaggtgacc tatagacata 360
cgaacaataa taataaaaca aaacctaagc cactc 395

<210> 231
<211> 178
<212> DNA
<213> Homo sapiens

<400> 231
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tcatctgact ttgccttgga gtcagatggg agaatgactc ctggagaaca cttagccttt 120
tccagctttc cccaanaaag gctggcccag ggaggcttct ataaaccttc tccctatg 178

<210> 232
<211> 299
<212> DNA
<213> Homo sapiens

<400> 232
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ncaagactca nagtcanaaa gacgtgggtt tcaaccttag ctctgccaat gactggctgg 240
acaagttgct tgctgtaagc ctcatctccc tcctcaataa aatgagtgta ataaccccc 299

<210> 233
<211> 137
<212> DNA
<213> Homo sapiens

<400> 233
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gaccaatcta gcttgaactt ttgactttgg acttcaacct ccagtattgn aaagaaataa 120
atatgttttc aaaagtc 137

<210> 234
<211> 216
<212> DNA
<213> Homo sapiens

<400> 234
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cacctcattc tctcaagtag ctgagactac agggatcgaa agatgaagaa ctcttgttga 120
agctcataac tccctaatta cttattatta acagtgaaaa tctgattttc aaagttgttt 180
aatggtcatg caataaagca atgtaagacg actgcc 216

<210> 235
<211> 281
<212> DNA
<213> Homo sapiens

<400> 235
gtctttggac ccagattgga actataccat tggctctcct gggtttcaag cttgcttgct 60
gactgcagat cttgggactt ctcagcctcc ataattatgg gtgagaagca ggagctcaga 120
gaaggtaaaa gcatcaaaat caccacagca acaaagattt ctcaggaaat tataaatgct 180
gagaacagtc ttgtttttcct tgcgttggca ggtgactcac tgcatagata tgatcatctt 240
cagagcctca ttataggttt agcaattaca ttttaaaaat t 281

<210> 236
<211> 491
<212> DNA
<213> Homo sapiens

<400> 236
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tcccagtgga tggtacacac atggcaaaag gccaagagta gaagcaccgt cattaggaaa 120
aggaatcagc caaggtccca ggcaagaaga ggtgaggcaa atggaggctc tgaggaaagt 180
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agtatgcaca caagaagtaa aaaaatatat ccnagtagaa aggaagcttt tcattgaaat 420
gnccccagaa ctcatgctct tgganggccg ggatngcaaa atcaagnntt tttttaaaaa 480
ctcctacccg g 491

<210> 237
<211> 199
<212> DNA
<213> Homo sapiens

<400> 237
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taaatctgtt tctatatcc 199

<210> 238
<211> 282
<212> DNA
<213> Homo sapiens

<400> 238
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gctatgctgt gtgacctcag gactgggccg actgggagca ccatgtggag aacagagaca 120
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agcaaataca agtggtcatg caggaagaag agtgctggtt ctgcggggtc ctaagaggga 240
gatgtacggg gggtgtgctt tgttcaatat gacaacacta cc 282

<210> 239
<211> 206
<212> DNA
<213> Homo sapiens

<400> 239
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cgtacattgt gacttgttgc tctcaccatc aacaggaatt gggctgtgca agcaattctg 120
aaagaagtgt tgtctactgc tgtgaaagtc atcaacttta tcagacccca gtcctgaccc 180
cagccttttc aagaaatttt gtctag 206

<210> 240
<211> 472
<212> DNA
<213> Homo sapiens

<400> 240
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ctcagttcca ttttacagga tgaggtgaag acttttcaaa gccagagctc taccctgata 120
gcacaccgtc aggatgttca ggaagagcct catgggttat tacagctcag gatgcatcca 180
gacactgtct ccatggcctg cggagctgct ctctgaggac tcacttcact gcccctcatt 240
tcccaggctc atggagatat actacctgtc acctctgggc ctggagggca gatggaggta 300
agatgcaaag gaagactgcg tcgtcaaagc agatggaagc attccctaac acctgggcca 360
tcctgggtcc taacttaatt actaaagaat aagggagatt tcaaagnaaa atgnncagac 420
atttgnttat ttgaacataa aactgggggc ccnccaccag tattttggta ac 472

<210> 241
<211> 283
<212> DNA
<213> Homo sapiens

<400> 241
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agtatagctc tgcaagcagt ggctacggac agtttccaac atgcaagttc atctccgacc 120
ccacttcatc attcctcctg cccccagcac tcctggatgc tatgctgaat tgttttggta 180
cctttggttt gtgagccttc ttaaaccttt ctttcttcta ctttattatt atcattgtat 240
tataaaagca atagatgctc attactttaa aaaatgtaaa agc 283

<210> 242
<211> 193
<212> DNA
<213> Homo sapiens

<400> 242
gcactgtctt cataagtcca caggtctcaa actccagcat ctcagaatga aaggattcac 60
aagtgctcac aagaggcttg gctgccaggg gaagctccga cctgaagatt tgaactaatg 120
agggactata aaggccaaga ccttgttctt gccatttag agattcagaa tataatctac 180
aaagttagag att 193

<210> 243
<211> 501
<212> DNA
<213> Homo sapiens

<400> 243
cctgcagagg tcanggagag agcccgatgg cggtcttaat gaagaggaag gaggaaagga 60
cgcagctttt tttacccccc ggcttaattt actccgtatt cggcttaact tactccctat 120
tctacccctcc ggtcttcaag ttcccttaag ctcgttggcc tgttacccag taaaactaca 180
aggaaatggt ctgtgtggtg aattttgaag ctgtccacag tacagatact ccagtgtctg 240
ccctttccaga aaagagctgg acctaagggg tcctcctgtc tcacgtgcag actcccaggg 300
cgggattaaa aaggcaaaaa tccnnngttt cntngcaaat ccnnggnant nngggnnnga 360
nntnntnntg ccncnntttg gganggaang aancanaatt aatttngggg ctntaaaggg 420
tttatttata aanggggcttn gggnttctat tttattgggg aanaaatncc gggganttaaa 480
aatntaaaga ccccccttcca a 501

<210> 244
<211> 327
<212> DNA
<213> Homo sapiens

<400> 244
gttcttccta acaagaagct acgaagttct tattcagaaa aacggaacac gacatcacac 60
ccacgtgaaa aaaacgcttt taagaggcca agtcactttc acctcccacc aacttgccaa 120

aggctgaaag caggcggaca cgcccccaag cgctcttctc cgatttcatt ggttgccccg 180
gcctgctcct cattaggtct ctctcactgg tcagcaatgc cgctttcaca gccaattctc 240
agaaccaatc atctccaact attgccccgc ctctccacca cgtgagtggc ataggtgcca 300
accaataaaa aaagaaaata aggatgt 327

<210> 245
<211> 100
<212> DNA
<213> Homo sapiens

<400> 245
gcangggcnt ccngnggttc aagggtacaa taanctgcga ncgtgccnct ganttctacc 60
tgggatgaca gagtgggacc ctgtgccaca aagagagacc 100

<210> 246
<211> 505
<212> DNA
<213> Homo sapiens

<400> 246
aaggctgtct cctgcgagga ccagaagttg agccaaggca cgtggaactt acaatagcag 60
atggtaagaa ccagggcaga aggagaactc ctgaagcctc cgaaggaagg aaatcattac 120
agggccctac agaagtaggt catgtgctac agctgctcat agtttaagag gaagaaacat 180
gggatctcaa acctggaaca cgactctttc aaaatgcctg tgagcaaccc aagaaaaaca 240
tcctcctgag gcttatctaa taaccatgat ctctaatcgt ctcaatgtgt gctcatgttt 300
ccttaagaag tttgcaccca cttctcagag ctaacgagat gccgaaacag aacacagaaa 360
aaagtaatga aggagattta ataagntgng ntaaagctna tatgggccat taaggggcng 420
gcttttttta aaacaanggg gnggaaccgt tcccctnttt tttggnggaa aagnnttttc 480
nggggcangg acctggaaac cattc 505

<210> 247
<211> 139
<212> DNA
<213> Homo sapiens

<400> 247
ataaaatctc ctggcagaga aaatggacag tcgttccata ccatatgtct tctcagcttc 60
aaaatcaaca acaacaacaa caacaaaaaa ccccaaaact tccatcatct gcagaagtca 120
aataaaactt tcaaacttg 139

<210> 248
<211> 261
<212> DNA
<213> Homo sapiens

<400> 248
ttgtaaatta tgctcatgaa aagagacccc agcatctttc aaactgangg ttaaccttat 60
tatcaggata atcaccaatt cacaggaagt tgcaaggatg gtatggagag cttccattta 120
ttcctcggtt ttccccaatg attacacctc acataactgt acctcaggaa actgaagctg 180
gtacagtgtg tgtgtatagt tccatgccat ttcgtcttaa gtgtagatct ccaatcaaat 240
aaagaaatat cctgtcacca c 261

<210> 249
<211> 241
<212> DNA
<213> Homo sapiens

<400> 249
gtggggtctt tcagtatgta caaacataca tgattcagga taaaagatgg atcgtacccg 60
ttctcaccac agaaaagtaa ccggagactc ttctaagaaa tcgagaaaag aacgcccttt 120
ctcctgccct cctgtctaaa gcgcaacata ataatcgaat ctcccaagct tcttagggtg 180
ctgagtgttt taatccacca gccctcttca actagttaat aaatcctttc cagaccgaga 240

g 241

<210> 250
<211> 505
<212> DNA
<213> Homo sapiens

<400> 250
gnaanctgnt agnncatgcc ngacaccttn tctccatgcc tgcnctttct gttccaagcc 60
atntggtgga agcaatccaa ttgcctgcag aatcatccga aagcatcact gggaagaagc 120
tggtggaact aagaagcaat tctttagcct gacagccagt ctgtttttag tatttctaaa 180
catgaaatca tctcaggaga agccaagggc tgtcgaggtg atttgcctga ggtcctacaa 240
ctcatcactg actgtgtttg gaggaaggaa gtaattaact ataaatgtga ttataagggt 300
ggggccttaa tctgatagga ccagtgtcct tataagaaca ggaagtgtgt gccgttcact 360
gaggaaaagc catgcaagaa cacaaagaaa angcggctgt cttgcaacct ngaagaaaan 420
ctttgcctaa aactaatcct gccgggcatn ttaatcttgg naattccagc ctccaaacag 480
nganaaataa aggctggtgg ttatg 505

<210> 251
<211> 90
<212> DNA
<213> Homo sapiens

<400> 251
agaaacaaat acatcaacgg agacaacttt ggaaacaatg gaaacaaaga accaaaaatg 60
ggcctgcaca taaataaaaa ctccatatac 90

<210> 252
<211> 589
<212> DNA
<213> Homo sapiens

<400> 252
aagaaggggg tttccgccat ggttngccca ggctggtctc aagctcctga actcaagnga 60
tcttcccncc taagcctccc aaaagngctg gggattacag gcatgagcca cgactcccag 120
cctgaaatat annattttaa tcttcagctt gcattttgtt ctaaacaact tgttttcaaa 180
taagaaccgg gcagaaccaa gtttaagcca ccatttgttn ggaggccaga atcaatttta 240
ttgggtggtg gttccaaaatn gggaactggn actaagcctt ccttcttccc ctccatcctt 300
cctagcccat tgnngcangg gggaaatttt tctcnttttt tggnnggggg taaaacaact 360
tctttccctc attctgggaa ttngcccttc aacctaattg ttggacaaac cgaaaaaaat 420
ttcaaaggcc ccccaaaaaa taagcaaggc aaggcttacc attaatncct tttggcatgg 480
aacaanggag gaaaattttt ttttggcctt aaanggnttn gggggcctag ccaccttgaa 540
aaaacaanna nggcccgggt tnacctttcc gaatcntggg gggcttcca 589

<210> 253
<211> 498
<212> DNA
<213> Homo sapiens

<400> 253
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gcggnttntn ttggngacat cacgggnccn ananaaaatg gnttaattta tgtaacaaat 120
cccctctgga ggacaccana actgnngggc cccttnttg ccctnatccg cngaaagnag 180
cccgaatgac cactncccag gtnccaacag cananggggg ggccnntcna aaaacnagga 240
ctgagaggag ggacccccg gctttctggg tcctgcnggg gctcacaaaa gttgtgaaan 300
tcatttattt tcttgcntca agacnttctt ntgtgctggg gngaanaaaa attgaaacat 360
atgcttaaa aaattctaac aaccacggag ttgngcattg tgttttnttn ccccaagaaa 420
agcttttaac agnggaaaaa tttgnttnta agcttncctg ggggctctnt tcctggggtn 480
cctttccttt tccctgaa 498

<210> 254
<211> 303

<212> DNA
<213> Homo sapiens

<400> 254
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gtacaagctc gtctgaaaag agttggcttg caaatgggag aagctgtcca agaagtattc 120
tcacaatgaa ataatcattt tattttgtcc ataccgacaa acaaccagtc aattcagctg 180
gaggaaaaaa caaacaaaca aacaaacatt ttatttttcca aatttgtaat gagttcgctt 240
aattattttt ggtttattgt gttatctaca tagttgaatc ttaaatctga attttcataa 300
ccg 303

<210> 255
<211> 441
<212> DNA
<213> Homo sapiens

<400> 255
caggatggcc tagatttcct tacggcatcg aggacgagat ccaagacagc aaaagcagac 60
tcngccaagc ctcttaatgg caaggccctg aagcagcaga gcttcacttc tgccacctcc 120
tattggttaa agcctgtcac aaagcctgtc gagattcaga aaaagagaga tagaacccac 180
ctcctgatag aaaaaagctg cacatgcata aagaaaggag aggatttgac agctatcttt 240
gaagagtatc tgccccatta agccatggga tattttcccc ataaaagaaa ggactatgat 300
ctggattgta gaaactgatc tatagacatg aatctgaact taagagaatt tgactaattc 360
catctgntca aactggcatc actcacacat atttctgnaa ggattcactc ttccatgggt 420
agcctcaata agaattcatg g 441

<210> 256
<211> 431
<212> DNA
<213> Homo sapiens

<400> 256
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aagggggggt ggcataccag cttaaagaac tgtgttcnnt tgnctgcaac cctgnagtac 120
anngnatnng aagncccatg ctgctctgan ggcgtcggaa tatgngancg atccttgcct 180
cctactanac tctggtgcag ggctgcanat ccacaaagcc caagctgcag caagtccgaa 240
ggcgcnccgc angggagtt ccttctcagg agactgnggc tttgctctta cggccttcga 300
cagaatggat gaagcccccc ccccctntgg anggtaaccc gctgcattca aaggcnaccg 360
antnaactat taatcctatc tnaaaaacng gcttccanaa acaaccacac ttgtgtttga 420
acaaaaactg g 431

<210> 257
<211> 332
<212> DNA
<213> Homo sapiens

<400> 257
gagcctntnt ccctggcaaa tgggcttcac tgttcatcac agaaacctcc tgaaggaccc 60
atctactctt caatcaacag ctggtgccct acgattctct gaatcccttg cctggcctca 120
aaatccctca cctcatggct tccaccagtc ctggactact gtgttcctta cacaacccta 180
accaagcccc cacattgaca cacccacctt aaagagnact gctaggcttc agaaaaccca 240
accttgcctc cttcctccca gacaggccaa agccctctgg aatcagcgcc ctcccttcgg 300
caagtgagta ataaactcag ctttgcctta cc 332

<210> 258
<211> 309
<212> DNA
<213> Homo sapiens

<400> 258
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cttcagaacg gaggcacaag gagagatgaa tgccacatcg caaggagcaa aggagagaga 120

gagaaagaaa tggtgtcagg tggcatgttg gatgtgattt ttgttttagt agagattgag 180
atgactgtaa attgtttagc tgattccttc ggtctgcaaa gatacatttg tgttggtgct 240
gatggttctt gactaatcct gtttcaatta caaattggtt atgtttttca aataaaactt 300
ctggcactt 309

<210> 259
<211> 427
<212> DNA
<213> Homo sapiens

<400> 259
gctttggaag gagtttaaac cttaagctta ccctttcaat catccactac cccagggaca 60
gaaggtgggg aaaactcaaa ggcacangct tgtactgaga agtttttgagc aatggagaag 120
aaagtgggag cttctgactg accttagccc accacagtca ggctncaaga ngggagatgg 180
cctgggntna tggctgcctt tcntctggtg nnccttacct tttgggaaaa cccccanggn 240
nagaaaagtc ttcaagtctt gtcagactgg gaagtcccca actcccaacc tnaggaagca 300
gcccttggaa angagaagga tgagatttc caaagctatc tcttaccact ttcttnccc 360
catctcattc cntccatnta ttggggagaa gnccctctnaa gttnggcctg angcttctga 420
gggattg 427

<210> 260
<211> 478
<212> DNA
<213> Homo sapiens

<400> 260
acatggaaac tgaggaacag agagatcaca tatcttgcac aaggtcctac agttggagag 60
agaatgacta tttcaacaat ggcaaatagg gttcatcatg tatgcacact ctgattgctt 120
tgtggtggct tcctggatca ctgggttgaa aaagacccag gctctgtagg aggtggttga 180
ttaatgatgt ctgccattca gaacaaagat gtagcagcag gtgtacctca tttttgctgt 240
ctctggacta ttccattgaa gcctttagtt cctggattat ccaattagcc ctagctttcc 300
tggcagtgtg atctccctct gccttaatat cagccctcag ccctcgggat tcttctctct 360
gatatccaca ctcattgcct ttgcttctct gngctcccta aaacaacgac ttttcttccc 420
caagccnaat tggaantaan tcctacctcc agngnganac tggccccggt cggcagcc 478

<210> 261
<211> 412
<212> DNA
<213> Homo sapiens

<400> 261
gaaagtagcc aaatcacctc cctggctctg gaagggtgtg gaagtggtgg agtaagagtc 60
ccagcccaga taagggatca ccaccagaag atgaagaaga tggtatgtcc agagatccaa 120
aggcaatgcg ggcctcacag tagatgccag cacacagtgg tgacaaacgc ttggacaaaa 180
cccatcaatc tcatgaacag cagagaggag aaacattgag tgaggatcag cagcctccta 240
gagcactagg ctcctgcatc agtctcctgc aacttagata ccaccttgag gtcgggggtg 300
gtgacaggtt tcattgtcaa ttgatgagtt tgtttcaatc taaaaaaaat taggtggggc 360
ccagaatgaa ctaagatgat gtttttctgt cttggagggg accgggcctt ga 412

<210> 262
<211> 389
<212> DNA
<213> Homo sapiens

<400> 262
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tcaaacctca catgtctcca cttgaaaagg atgagtttca tggaacctga gcatgcccat 120
atgcccctac tcccttgtgt gcccccacac cgtgcctgct cttccttcag ttgatcaggt 180
gaaaacctca gagtcacttt taacacctcc atttctctcc tgtgccaaca accaaattat 240
atccaaaatc tgaccacttc tcaccacttc cacatggact gctgtgttca agccaccacc 300
atctcttgcc tgcattagtc cagcagtctc ctanctgaca tggggactga gattcagaat 360
atttgggatc aaaggtctta tccctgaat 389

<210> 263
<211> 298
<212> DNA
<213> Homo sapiens

<400> 263
aatgttaacc acaggacgtt ccagctgtga ctcattgcaa ctactgacaa gcaagctgga 60
gtggccctgc ttttagagag cctgaagatc tactcagagt gaacaatact tgaagttcta 120
attgagttac agaaaggaaa ctagtaaaaa ctaagaaaga ttgcgattct caccttgaat 180
atgcagatct aatttctata actgtgttta ggggtatttt tctaaattac taaaataatg 240
cttacatttt caaattggcc attaaatata tcttcagatg cggagatgtg tatattac 298

<210> 264
<211> 470
<212> DNA
<213> Homo sapiens

<400> 264
acagagctct gcaggcacag ctgaggacgg cctctctttg ggtcccccag actcatccct 60
gggagctcac aactggcaga gggagacaag ggcgctccaa gcagcagccg tgggggagtg 120
gtgatctcca gcttcaactg ccgggccgtg aaaacaggaa ccagccctcc aggccaccgt 180
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agcgaggcag ctgtgcttct cagtgccccg tgccgtcctc agccccatct ctggcacaag 300
tggtccaagc agcccaggac tccatggcag gccctaccct tgcaggtgaa ctgcctcggg 360
tctnccagcc tccacattca catatttcaa acagaaacac caccaacttn ctgggctnac 420
ccnttgggaa attccccaan gaaaacaaag ggggactcat atttgggcca 470

<210> 265
<211> 202
<212> DNA
<213> Homo sapiens

<400> 265
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aatgaccttg ggctatgttg gcaaagcaca atgggaagaa gacaaccaat tgaaggtcaa 120
actaggcctt aaaaaaaatt gttcttccta aatgaaactt tatgtaagac ccaaacttcc 180
tttatgtaaa aataggatac cc 202

<210> 266
<211> 258
<212> DNA
<213> Homo sapiens

<400> 266
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tgggactcag tcttcctaca aggcaaaaag agaagacctg gatgctccac gtggtccaga 120
catggagcaa gtaaaccgag ctctcgccac acgcacagt ctcctcagcc tcctgctcaa 180
tgtgctttca ttggaaatgc ttattgtaaa tgatgacact tttttaaaac caaaattcaa 240
ttaaattcaa tacatatt 258

<210> 267
<211> 320
<212> DNA
<213> Homo sapiens

<400> 267
gataataaaa catgaagtgg aagatcttct agaccagcac cttaaatttg cagatgagaa 60
agttggaacc cagaaaggct gagaggctca aggtctcaca actgtttatg ctcaactggg 120
aaatgaattt gtttctctgg cccatcaggt caacatttctt tccactcagc tatgccgnct 180
cctacctcct gaaaagattc tagcaggacc ctctgatgaa aaggacctta tctttttata 240
tctgctgttt aaagcttttt tttaaaatca tcgcacgatt ttatgagtta agttatgtac 300
ataaacaaat actattactt 320

<210> 268
<211> 498
<212> DNA
<213> Homo sapiens

<400> 268
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cagttgagcc tgggctacgc tgacacagac tttgttgctc ttcatttggc aaagttcctc 120
ccagaatccc tgcaggcata caacagatgt tcagtaaaca ctcggttgat gagaactctg 180
ggaagacata gctgttcgac gaacaggcat cagaatttat catttgaaat tatcaactca 240
aaaattcttt ttttcctcat acatattctg cttatgtatc aaaaattatc ataagaaacc 300
aagatttctc agaacatgtg aggtcaaaat ggcttataat gtaaaagaag tggagtctca 360
atctatactc agtatctccc tctcttttat tcatacacat atggacactt gcacttctaa 420
gaaaaaatga attttttaa actcattcat ttattaaatt gatatggatt aaaccangna 480
atattcataa catattct 498

<210> 269
<211> 342
<212> DNA
<213> Homo sapiens

<400> 269
cntctctgga gagcttncat ctgcaccatg agcccatgcc atcttctgac tcctggagct 60
acagtgaaga tatattttgt attaatgctt aacttcttca tttcagttgc cattgaggta 120
gcctaataac attcataagt aaatactgga ttttagtttg caatagaaaa accttccatg 180
taatataata tgtctataca attaataatt aattactttg ttaaaatatg tatctttaaa 240
taaataaaca ttggtagaga ccaaaaaaaa aagaaaaaaa aanggccacn gnggccaatt 300
cagctnggac ttaaccaggc tgaacttgnt caaaaggggg gg 342

<210> 270
<211> 159
<212> DNA
<213> Homo sapiens

<400> 270
ccagcattta tggatcttca gaggnttctc tctgtgataa ttcctcatca aattaccaat 60
aagaaggata tgaaactaca gcccccacaa ggatgcctgg tgaccttcgg ccctgagatt 120
tacagtctgc ggaagcaata aagttcctct ccctctctt 159

<210> 271
<211> 521
<212> DNA
<213> Homo sapiens

<400> 271
ggcaccgcaa gacaacgtat ctcccctccc ctgtgcaatc agtcaaagaa catttagtca 60
acctgaactg ggagcacagc gctcctgggg ctgttgggca ttcaaaagag tgtggatcag 120
tgttaaaagt gcctcatgga gaaatggagg cctgaaagcg actctgaagg aggagtgggg 180
ctcagcaaac agcagacgag tttcaatcca agcacccatt acccccctaa cacacggcat 240
acgtgcatct catctcctcc tgtgtcgcta agaagctacc catatgtctg tcattaattc 300
tccagaatcc ttggacacac ccctctgcag agctttctaa cagaaataca agtctcagat 360
ttttttttaa gttaaaattg agtgcagcac tcataccttt cttcgagcat gaaccgtcaa 420
tcaacactgc ctcatgagct actgntctcc tgctctttaa aaagacaaan ccttatttct 480
ttgtagngat cncaaagngg ngggattnac ccggaaactt t 521

<210> 272
<211> 460
<212> DNA
<213> Homo sapiens

<400> 272
agtttcactc tcagaggagg attttgttct tcaattgtgg agtgatctct atcaccagtg 60

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actaaagcag atgttggagc acagagagcc ataccccaaa atatgatgct tcggcatgct     120
gactgctttg aaaattgaaa ggcctcagaa ataatcctca gtgccagggt ctccctctga     180
cctccccctа cctccccttc tctctgatcc tgtctctccc aaagcacaga atgagctgtt     240
ctctgaattc ccttatctac ctagaaactg gacccccaaa gaggaacaca atttgccttt     300
gatcccttcc ctgaaatttc attaaccaga gaaaattaaa acttctatca caaggaagag     360
actgaacatt aaacaccata gctacagccc agacaaactt cttcccaaac cattgtttgt     420
tctcctgcct gttaaattgc cagagaatca ttcacaagac                           460

      <210> 273
      <211> 224
      <212> DNA
      <213> Homo sapiens

      <400> 273
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cctggatgcc acatggacca cgatcaccaa ggagatcgat aaatcccaca atgttgttcc     120
ctgtcttcaa aaatttgtca agaagattga gatccactgc tgtaagatta cacagatgcc     180
ctcctcatcg tctatgacag gctataataa atcttgccag actt                      224

      <210> 274
      <211> 338
      <212> DNA
      <213> Homo sapiens

      <400> 274
aggcgagaaa ctgtgggata agaggctgca gcaattgcat gagtagaccc tgaaggtatg      60
aggtttgtta aaatggatgt tcagagaagg cctgacacaa gagggccact ccatttgtcc     120
ccacggacct gggccggatc tctcaatttc acactgatgg agcctgaaaa tcaacaaaca     180
agacggcaag aacagggaag acattgttct ctccaaagtg gacaatttgt gacaggccca     240
ggaaggctgc ctgggcttta tagcttttcc agtggttcct aataaaccag gctttgtgtg     300
agcctcgttc aagccatgcg gggccctgtc gtttcttt                             338

      <210> 275
      <211> 158
      <212> DNA
      <213> Homo sapiens

      <400> 275
tcccaggtgt atccaccagc tccgaagaga cagcgaccan gcaagaacgg gccataacga      60
cgatggcagc tttgtcaaaa agggggatat gtagggaaaa gagagatccg actgttactg     120
tgtctacata gaaaaggaag acataagaaa ctccttttt                            158

      <210> 276
      <211> 144
      <212> DNA
      <213> Homo sapiens

      <400> 276
acttcagttg acccaggcaa ctgaaaccga ggaagcaaaa ccatggaccg tggaaagaag      60
catcatatag gactactgta ttatgtatta taggtggctg tggtatcaac atacttagtt     120
gataataaaa atgtttgcaa agtc                                            144

      <210> 277
      <211> 561
      <212> DNA
      <213> Homo sapiens

      <400> 277
gagcccatca tggcgacgcc ccctaagcgg cgggcggngg aggccacggg gganaaangg      60
ctnggctnca aaactttant antgancngn ctgcacggga ctggcgaaan ggggctgaac     120
catcgaaaca gggtattatg aagccagctg ggccaaatac cttcaactgg agaaaatggt     180
catttgagcc gaacttncag ggaaagctaa agcactcggg aagttattat atgccaggtg     240
```

```
ggattttggg cctggtaaac tttcttcgtt tggacacagt gggtccccaa gataccttttc     300
acgccatcta tgtggccccc ggggaaaaat ggtttttttc ctggaggttg acacctgggc     360
aagaaagcct tctaaagttt catttgattc gtaaagaact ctctcctcac aagaagcttc     420
aagcaaacag ccctcaccca agggactcca tgaaatatca aaagcccata tccacatgtt     480
gctagagggg cttaaaaaac tacaaggggc tggagaaatt tncaaaaaaa actcaacatt     540
ggctttttttt ccccctactc a                                             561
```

<210> 278
<211> 338
<212> DNA
<213> Homo sapiens

<400> 278

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tgtaagctcc accagagcag cagactctca taaaacctca tgggatgaat gaaaggagtg      60
tcatcccctta agacattggc aacaaaagca tagcctgaca tattctacta caagtgcctg     120
cagtaaccta tgcagagagg agcaaatgaa ctcccacagg aaggtggacg atccctgagc      180
cagagataac tggaactctg gcagtttgag tggacactca gtcacacact cacacactca     240
ctcacagcgt tatgcaattc caaaaattat gtgtttggtt ccaggaagat acatttttcc      300
cctctaagtc caaaataaag atagaaatgc atatatct                             338
```

<210> 279
<211> 271
<212> DNA
<213> Homo sapiens

<400> 279

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gttcccagta gctgcagcag tgaaagacag tgattggctc cagtgctccc agaaggattt      60
gggctgaagc caggggaaca gaaccagaag aggattccct ttccagagac catcaggctc      120
ctcatgtctt gtctctcctc tctcccctcg tggtggctca ggatttcagt atggctgagc      180
agcccatagg taggcctcaa cacttggtgt caccacttca gtctctatat gtttggccct      240
tgtgtaaaat aaacaaaaac ttgggcaacc c                                     271
```

<210> 280
<211> 490
<212> DNA
<213> Homo sapiens

<400> 280

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gagctggtca gctctgacct ggagtgtgtc taccctgacc gtgtgacacc gggatcaaga      60
ccctctcctg gggtcttgag gacgccacat gtgggcgttg ctctaaagag cgcttgctcc      120
taagcctcct gcacatggaa ccccaccatg gaatctgctt cccaggaact caccctggga      180
ccagcccctc tgagactcaa gtcaacattt ggtcctaggg ctgcaaagag gaggtgctaa      240
gaggccaaag gctacttcca cctggagaac gggccccgcg tgccagctcc cccaaggcct      300
ggccaggatg ctctgctcgg aggcctgtcc tgacttcctc tgctcattgc acctgaaatt      360
acctaaccaa caccttttct cctcccaccc ttccacaaat acttattgag catctgctag      420
gtgccaagtt actggtctgc acaatgggca ttacnggccc tgaaagaaat taaacnggaa      480
ccttcttgtt                                                             490
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<210> 281
<211> 512
<212> DNA
<213> Homo sapiens

<400> 281

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gaggtgattc atcccaccag tgcttcttct gcagacagta aaatatggtc ccagtgacca      60
tctcaggtgc catgcttcca gcatttttatc agacaaggct gaagacagca gacattaaac     120
ttcagttgtg tgctccacag aacattagct gtcttcatca ttactttgca tctttcagtg      180
ataggctgct tgacatgtta ggaacctgaa aatgatccca tcttgaccga atctcaaatg      240
cccttcctga gcagcactga tgaaacagat ggagcacctg gatgttatct gctttggatc      300
tggttctcag gaggaggagg agcagaaggc tgggcacaac ggtgtttgag gttctcaact      360
gccccagaa agaagggttg acttgattta catttgacttc aacttgatta tcttgatcta      420
cttaactggc ttttcggctt ttatgcttca agccnccggc angantggct tccttntggt      480
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caacttgcan gnctttgac ttgggattta ac 512

<210> 282
<211> 393
<212> DNA
<213> Homo sapiens

<400> 282
gctgtaagct ccttggaggc aaggattctg tctgcttcac ctctaaagct tcagcatggc 60
atgtgccctg caaatggcag tgccagtgga catatgctag atgagtggat gaaggaccat 120
cccacatcag ctcatcgtgg agtatgcagc tcagtcctcc cgcctctcag ggacaacttg 180
gatcttcacc gttcttcgcc actaagaatt cnagtcatct acattcagag ggaagctgag 240
caanctggct cctgcccaca ctggaaaatt tctctgccta aaccagcttc cctaagccga 300
ggggagagtc caagatcccg aagatggcag ggccgtgcag gctcctggga ttaagacaca 360
aacaagccct gttctcaggc tgacagtaaa tgg 393

<210> 283
<211> 139
<212> DNA
<213> Homo sapiens

<400> 283
ttactcatgt cagtaagcgt ttactgagta tctcctgcat cctgggcact tctccactcc 60
aatgtgacag cagtgaatca aacgacagct agccctgccc gcaggcactt gcattccaga 120
gagaggagac aaagaatac 139

<210> 284
<211> 482
<212> DNA
<213> Homo sapiens

<400> 284
gtccttgatc tctgtggctg tgagacgatg aatctagggt gtcaccccag acaacgaggc 60
tgcttcaaaa tcccaaagtc caaaggagga ctgcttcata agggaaggat tgtttatagg 120
ttggtatact gtgcaaaatt aagtatagga ccaaaaacag ccaagacatt tgaaagttgg 180
aaagttgatg gtaatggttt cctgggattg gaaggcagac ctcctccgct gatgagcaaa 240
taatgaggct gtgctatgat caaggcattg tgacccctgt gacccacacg tacacatcca 300
gaaggtctcc tggagccaga aagtctggga caacaggaaa accacaaaag aagaaaaaca 360
gctcctgtct tagctgatta gccaaccttg cgaccttcta ccattggaac atgctctacc 420
cttacttant aatncacttt cnggaccntg ggctntgtga cccctcccc ttgggataat 480
aa 482

<210> 285
<211> 241
<212> DNA
<213> Homo sapiens

<400> 285
cctccatgct ctgaggaacc ccaagcagct catggagagg cccacatgga ggggaagagg 60
agctcccagc cagcattcaa cttgtcagta acggaagtga accatcttga aaggggatct 120
tccagtctcc aatcaagccc ccagcccaca ctgcttggaa cagagaagcc gtccatgctg 180
agccctattc aaattataga ttaatgagcc aaataaatga ttgttgctgt tttaagccac 240
t 241

<210> 286
<211> 222
<212> DNA
<213> Homo sapiens

<400> 286
gaagtgggaa tgatgcatat tcaacgacgc ctacaaaaat tacttcagat tgttagtctc 60
agaaacccac tggtggcctg aggggacatg caaaaagaag aggaacagga gcagagatgg 120

caaattatta aggtttcaag accttaaaag agacaatcaa agtattcaga ttctcagtaa 180
aattaccaga ttaaatcaaa taaaacccca ccctttttcc ac 222

<210> 287
<211> 280
<212> DNA
<213> Homo sapiens

<400> 287
attaaatcaa gattatgtct gacaaccctc tcaaaatgat aaaaactaat ctgcagagaa 60
aactggctgc agaggaaccg gctgcagagg aaccagctgc ttcctcctcg gaacatgaag 120
aggtgaacag agagatgaag cctntttntc ctccctcacg tttntgaang atcaaaatca 180
agggcancng ggagaaagaa taacaaaacc aacaaactgg aggtcaagga gagnttttt 240
ctttttttta cctttctgcc ttttccattt ttaataaaca 280

<210> 288
<211> 435
<212> DNA
<213> Homo sapiens

<400> 288
ggcttatctc cttgttgtat ccagaatcat atgacaagca agagtcctag aatattttat 60
ctacctaatc atcccactgc cttattccag aaagaatcta aggaggaatt tttatttctt 120
cagtcaaaag atgcaggaaa gacatcctac ctcttggaag aatcattgga ctggacatcc 180
aaacacctga gtcctagcct tgagtctgcc tctcacagca gtatgaccct gggcaagtcc 240
ttgtggaata agggcatgga cagaatgatg tcagaggttc cttctagctc taatattcta 300
cagtttcctt ttagttcaaa tttaaagaca aaatgtctaa cagtggttct tgtttgttat 360
gaccagtgtt gncaaaagag aagttgtaca aagtttttt tgcctgnttt tcatgnatgg 420
gggaggggg gggat 435

<210> 289
<211> 166
<212> DNA
<213> Homo sapiens

<400> 289
caaacaggaa caaaggaaca aagtgagagt ggagactgct gagtcatacc taggagaaga 60
ctgcaactca cccagggagt gagtcttcac cctaactcac cggggaactg gaccgaccca 120
gacaatttgt taagttctgt ttccattaaa cataattctg agtctg 166

<210> 290
<211> 507
<212> DNA
<213> Homo sapiens

<400> 290
gaatttatgt tgatgcagtt aactccttgg gccaaacagc acttttgttt gcggcgttat 60
tgggccttag gaaattcgtt gatgttctgg tggattatgg atcagatcca aatcaaatgg 120
gagccctgtg ttgcacgctg agccccgctc catggaatgc aggagcattg ccatggacat 180
caattgtact catctcctc cccagccgct gctttgatgg gagcacccct gtccatgcag 240
cagcattttc gggcaatcag tggatcctta gcaaactgct ggatgcagga ggtgacctgc 300
gactccacga tgagaggggt caaaacccga agacttgggc tttgacagca ggaaaggagc 360
gtagcaccca gatagtggag ttcatgcagc gctgtgcctc acacatgcag gccatcattc 420
aaggcttntn tttccaactt cttgaaaaaa aaaaactccc cgcaggggtt tgtttacagc 480
ccgtcctggn ggggttgggt tcttttt 507

<210> 291
<211> 192
<212> DNA
<213> Homo sapiens

<400> 291

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tgaatcgaac gccacactca ggtgagntga gaaaccctta ccgcgcgcac tgcaatgccc      60
tccccttcac tctgcaccct ccaccccct gaaattctgc ccttaggcta cggggcgtcg      120
tcctttcgca ccctccccca tgctgccaag ttgtagctat agctacaaat aaaaaaaaac     180
cttgttttcc ag                                                          192

      <210> 292
      <211> 408
      <212> DNA
      <213> Homo sapiens

      <400> 292
gtggtagaag tctgtcttct ccccgtgctc ctaggaagac cttcatgtcc tccttgacca      60
acaggggatg gtggaagtga ctctgtgtga cttgtgagac aagattctaa aagtcatgca     120
cttctgcctt gttctcttgg gataactgct cttggaaccc agccattgca gtgaggaagt     180
caaatagctc catggacatg ccatgtgtag gtgttctggc aaacagcccc aggtgaggtt     240
ccaactgaca gccaacgtca accacctgac gagaatgagt cttccagcct tgatctgctg     300
agtcatcgcc aactccagcc aatactgtaa ggagcaaaga tgagctgttc tgccaattgt     360
agcccaaatt gcagattttt gaataaaata aatgactgtt atcattgt                   408

      <210> 293
      <211> 316
      <212> DNA
      <213> Homo sapiens

      <400> 293
aagtctcagc catgaaccta gcagtgaagg aggaaaacat cttatgtctt gttctctaca      60
acacaaagat gaacataaag aagaaacaca gactctggcc tggagaagtt cagtgtctgg     120
tgggggagac tggataaata atttaaaaca tttatttaac acataattac agtgcaatat     180
gataagtaca atagctaaag tgtgggcaaa gtgtcgcagg aacaggaata aagaggagac     240
aacttccaaa aaaatcttac atacttaacc ttttcccgac attttgacct gaaaataaat     300
cagcataaca actcac                                                      316

      <210> 294
      <211> 149
      <212> DNA
      <213> Homo sapiens

      <400> 294
gctggtagca gaatggctgt tgttattcca agaggccctc ccggactata tcccagtgtg      60
tatagtccag tgaaacgacg ggaaaactat gaccatgaag caaatctgga gcaccacctg     120
attttttaag gtagatttta ccgaaacac                                        149

      <210> 295
      <211> 233
      <212> DNA
      <213> Homo sapiens

      <400> 295
gaaaagtgta ctggctcctg tcctggatca actcagaaaa tgaaacacat cggattctgt      60
ccaggccggg cacagcaacc tggcccatnc atgtggagcc tgcagtgaca acttccgcta     120
tctgcacaaa actggaggga ggctgggggt gctccaagta taagtttcct catcancaaa     180
ccggaaagag aaagaccgac ctggaggctg gttatgggga taaaataaat atg             233

      <210> 296
      <211> 143
      <212> DNA
      <213> Homo sapiens

      <400> 296
tgtacagagg aagaaccatt gtgaggataa agcaagaaga caaccgtctg caagccagga      60
agggaaactt tatcagaaag caactgtgct ggaaccctga tcttagattt tgtagtcttt     120
agaaaagaaa taaatattat ttt                                              143
```

<210> 297
<211> 201
<212> DNA
<213> Homo sapiens

<400> 297
gtgatactgt ggctgacagt atttactgtt aaatggagtg gaagtgagaa aacaccacag 60
aaggggcac ctanattcga accggggacc tcttgatctg cagtcaaatg ctctatccct 120
gagccctacc ccctctacct gtaataagct tcttccgtgt ccacctacgg tgactcaata 180
caatcaagtt ccacccacac g 201

<210> 298
<211> 77
<212> DNA
<213> Homo sapiens

<400> 298
gctctgatga ttcttaagca aagagatgga agatggaatt tcaaccccat ggagatctaa 60
taaacttacc cagagtt 77

<210> 299
<211> 452
<212> DNA
<213> Homo sapiens

<400> 299
atgaaaaaac tgaggctggn aganggccnt gcccctgccc anantcatgn atntgnccta 60
ngatggatgn ggaatnctgc cccaccantg gnggcnttat tattacaccc atattacana 120
tntagaanac tgaggctcan cntgggtncc ttgccatgan cacacannna gangatanga 180
gaggctggct ctgcctccta tgccnctcct gatccactct ccaaaccctc ctccagtccc 240
ctgctccaag ccatcagtta ggatgattct tataagccgg gggtgtgaca tgccaaaggt 300
gtctctaccc cacatactcc ctctggaanc aggacaaggt ttgcgtgagg tggacctggg 360
ttctttctgg accagggact ttgcctccaa gctcatttcc tcatctgtaa aacaggaatc 420
caaccaacgt cagcctgaat gggctgtggc tc 452

<210> 300
<211> 434
<212> DNA
<213> Homo sapiens

<400> 300
ttcctcatca gaaggaagta cttcatcaat tacgtcctct tcatattcat caatttcttc 60
cccatcatac tcatcttcgc ttcccacatc acttcctgac acctctgcct catcctccag 120
atcgcttcag gagttcttct tcatcatcat cttcatggtc ttccagtgcc agatcattac 180
cagagtcact gtgttcatcc tacaaaatca gcatcatatc caaattaagc agaataaaat 240
gcgtcctcaa tgaaaaaagg atttataaac atctgcccaa atacctcatt ctaggaaatt 300
gtttctgata agatgccaaa cttagaattc tcaagaactg aggggaaaaa aacacttgag 360
ggcagcaata catggagctc aantatgaat acctttggtc ccttctacct cccctnatcc 420
ttttcaaact catt 434

<210> 301
<211> 456
<212> DNA
<213> Homo sapiens

<400> 301
ctctcaatct ggggcatgac tttgaaggga aggttgctaa gcctcctaaa tcccgataca 60
caccaatgcc gtttccccac tcatctggaa acctggtggg ncctgcccaa acgcctgtat 120
gccaattcca cctggctgct tggcgaccca ccatgcccac attttccact caagcctttc 180
anatctgctt tgggcacctg aagacagaga gaatcatctt tcaagagtca gaaactttgc 240
acgtgccatt ccctctgctt agaatgcttt tccctttctc ccaattgcct tatcatcagc 300
ctgggaaaat atttatttcg gctcctaaaa tctcagatat cacttctcca ggagctttcc 360

cagatgcctc acttgattcc agaaggagct atcgccactt ttgcctggcg agtaccgttt 420
tcaccgttac acttatacgc tatggcaatt tattgg 456

<210> 302
<211> 187
<212> DNA
<213> Homo sapiens

<400> 302
tgactatatg acgtgtgatg gcccaagact gagtcaagaa gcagatgcaa gaatctagct 60
gactttcagg aaattagacc ttaaagcgac ttgcaaaaat gaaaaacgaa gcctcttcca 120
aattttttgt tttggaaaat tagttatttt tcataaaaaa cttacattaa agtatttatg 180
tcaaggt 187

<210> 303
<211> 449
<212> DNA
<213> Homo sapiens

<400> 303
tttcaggttt taggatgacc agtgagatgg tcagaacttc agaaccttcc aaggtgatgg 60
gtcattcaag ctccaggaac gtcaaggcct caacagtttg gacataattt taagcaacac 120
atataagacc cacaggtctc cactgatatg actggggatc tcatgaagaa actactcgac 180
aaagacagat actggaggga tagaagagtc tatgaagtac agaaaagagg aaagatctgc 240
aaacaattcg gtgtcttctt ttaacttgaa actcattcta cccactgcta cagctaggta 300
ctgtgctctt gctcagattg ctggagggtt ttgttgngat gatctccttc aatacatcaa 360
tactataagt tctataanaa tcatctcaga gcttgtttan aactcatttt ttttcttttt 420
ctgggntatg cccttataat attcattta 449

<210> 304
<211> 309
<212> DNA
<213> Homo sapiens

<400> 304
gtggggtctt tcaccggcca tgtccctggc tgactgtttt cctgctgatc ctgaccagcg 60
tcccggcag ccatggcctg cattcgtgtt ggtccctcct cctgcagccc cgaggaggca 120
gggctgtctg tggatcccag atcggttgtc ggaaggcccg gaagaggaga gctgccctcc 180
accaccactg tctcctcctc ctggacaaca gagtcagaac actgctgaga tggggtgaag 240
cataattgtt gcactgagac tcaaaactac aggcaagaag gtttgaaaat acagaaacat 300
ttcacgaat 309

<210> 305
<211> 174
<212> DNA
<213> Homo sapiens

<400> 305
gatgatgctg cccttaatgc tcagctgatt acagactaaa cacaaaagtt cccagaggaa 60
aatggtggac ttgggagctg ctgcctcagg aggatcttga gtgttagtgg ttcctcccta 120
tcagatgtac ctaatgccca ggatttaata aaggatcatt cccattccac cacc 174

<210> 306
<211> 464
<212> DNA
<213> Homo sapiens

<400> 306
gagccccttt cctggacaca ctcgtgtctt tcccagggaa tgggaagaaa caaaaggatg 60
atgacatgac acctaataag tctggatctg gaagtaagtt tgatctacgg ttcattaggc 120
tggagcagaa aaaaaagaaa gggtccggta tgttcgcctg tgtgccaggt atggtgttac 180
gccactcatg tgccttatat tccctacaac ccctcacccc aatttatcac ttcaaaaatg 240

ataaaagctg agacttggag aaactagtaa ctaaccaaaa gtcacccaag aaggaggtgg 300
caagctaaga tcaagcccca ctttggtggg agctaagagt agccccttggt agagtcatgg 360
ggttggctaa ttcttgcctt tggaacctgt ttctatctcc attcagttcc tttctttcct 420
gtcagttgga ctgtaaactc taagatcacg aaatttccct ttat 464

<210> 307
<211> 481
<212> DNA
<213> Homo sapiens

<400> 307
agctttgcta gccacgtgtg gttcctagac catcagcatc aacattacct ggaaagggcc 60
tcttacagat gcagaatctc tgccccaacc cagacctatg gagttaaaac ctacgggatt 120
tctagatgtg cgggagtgaa ggagctggtg gctatcagac ctcaaggtct ccaacaggac 180
aagatcaaga gggattccac tcccacagac cactcactca ccctaggaag actgtgaaat 240
gcctgtcctg gtgcttagtt tgaattgttg aaagaccatc tttacggcag aaatgctttg 300
tcatttcact tgataagggc cttgggtttc aagccagttt actcttttct gtgagcattg 360
aaagcccccc ttttnatttg ctccgaggca ggattttgac ttcaaagcca aaataagaat 420
ttaggaagaa aagaaaggga gggaggaaaa agggaagttt ggtccaggaa aatgaaaatg 480
c 481

<210> 308
<211> 177
<212> DNA
<213> Homo sapiens

<400> 308
gggcaaaccc atgctttatg aagcctgatg cttacacaat tatgggagcc ttctttgaaa 60
aaaaaatttc aaaattacaa atgcaaaatt aggtacaaaa gggaatattt acaatgagaa 120
atcaccacaa atggcaagat ttaaacagct gacaaattaa acagcgcaaa atccagg 177

<210> 309
<211> 366
<212> DNA
<213> Homo sapiens

<400> 309
gttgcaagaa agctcaagta gcctatggag aggatgcaag gcttccagct gatgccctca 60
gccaggctca gtagcagcca gaactagcct accaacgaac ctgctgatca tgtgcataag 120
ccacctttgaa cgtcgatcct cctgcctggt ggagccatcc cagctgatgc cacatgaagc 180
agacacaagc tgtccctact aagctctgct caagttggat attcatgagt gaaataaatg 240
actgttacta agtaattaat tttcgggtgg ctgttatgta gcagtagata attggaacaa 300
agcttattga cataatacat ctatatcaca tcctccaatc catttttttta agtaataaaa 360
gtggtg 366

<210> 310
<211> 292
<212> DNA
<213> Homo sapiens

<400> 310
gacccaaatg tgaataatgc caacagcttg ctgtcagccc tgaagtttcc tcagatgtct 60
cataaacact ggaatcactt cacacgtttc tgaaatgtga ccacctctca ggaggagttg 120
acaacactga gtaaccggaa gggaggaaca cttatcccac tgaaactggg ataaaggttg 180
ccatgaatgc aagaggtgcc taaatctctt ggcatgggga cttaatgggg ccttatccct 240
cctgctatat ggtagcaaaa taagaaaata aaaaccaaag taatatgcgt tc 292

<210> 311
<211> 195
<212> DNA
<213> Homo sapiens

<400> 311
atgaaagaaa gagaagtccc taagtagaaa ctgcaagggc caagcagaac attataccat 60
gtaaggacat catctgtccc tggactctta agcggaagat catgcaaata gtggactgaa 120
gtcatcccag ccttcaaaag agccaccgtg gggggggaaat aacagaaagg gataaaaagc 180
tgtctttcgt aaccc 195

<210> 312
<211> 475
<212> DNA
<213> Homo sapiens

<400> 312
aacagttctg gaggccggaa gtctgaaagc agtatcagta ggtggaaatc agggtgccca 60
gcttctggtg gctgtgacat tccttggctt aagctgagat ggcagtcaat gagagtgact 120
gcagaaagtt tcagaaggac acatgggaat catttaacca ggccaataaa atcagctatt 180
tatacacttc ccccggaaga catagccctt gcttcactgt ctgaaggaga gaaaatgcaa 240
aagtgataaa ggcatgaaaa agtcatattc ctgagctaca agagagaaac tgaggacagt 300
ggagatgaga ataaaatccc taaagcttaa aggatgctgg atctggattc tactggatgg 360
nggngcttna aaagnggact gncctatcct tttcacatat gttagaggtc acacacaggg 420
agcccacaga ccccagcatg ccaataaacg tgtttcttgt gacccataat aaatg 475

<210> 313
<211> 425
<212> DNA
<213> Homo sapiens

<400> 313
gtctactctg tgaaaaggaa atgatcatac ataattcacg catttgctgt acggatttaa 60
ttaaatgata gacaaaaagt agagtggcac aagtcaaact caaaaaatag taacaacaaa 120
atcaatttca aaataagcaa cagcaataaa tgttacctac tattttacga atgaaaatac 180
tgagaccaat aaaggcatta tagtatacat agccttggaa tcagaagacc aagaacatac 240
aagagaacat agccttggaa tcagaagacc aagaaacaat ttaactctgc ccctctagag 300
ctctgagaac ttgggcaagc cttttaccct ctgtgagttt cagtttcctc atttatttaa 360
ttggaatnat aattccngat cacctgaatg taatgaaaat taaacatcct tatgtaggtg 420
aaacc 425

<210> 314
<211> 478
<212> DNA
<213> Homo sapiens

<400> 314
gtagaagatt ctgaggccct gggcgggaac tagtaagcca caatctggaa gagtctttta 60
ccaccatgtg gaggagaact agagcactca tgttgaacta ttaccganaa aagtaatcaa 120
cttcttttgt gttaagmcac tgaaaggcaa gtgttgattt gttgcagnaa tnggggctcc 180
cttaacacac ctgtcagccg ggccaaactc tatcacagca taaataatct tttccttaaa 240
taaatacagg taaaagaata aagtagacct aaatgcatta atatgaatat aggctcaaag 300
caaaatgttg ggctataaat gttcagagtg ataatttttt aagttgatgn gtaatttagn 360
nccagtaaat tagaataaaa cctaaatgtc agttcaaatg gaatttttta catgttcatg 420
cccctgtata atcacctccc anaaccaaca tagaaaatac ttcatataaa atgttggg 478

<210> 315
<211> 325
<212> DNA
<213> Homo sapiens

<400> 315
tggcaagaca ctggcctgat agaccaggag ctactccacc accagcagct acaaggcctt 60
ggcagaatgg aataacagca aacaacattg gaggaggact tgtctgggag agcagccatt 120
ttaaagaaga gcacattaag tcacaaacag tcgcagctga tctactttgc agcatcgcca 180
tacatgccta actaaatatt gaaatcccgg gaaaaactca ctgtgcatca tgttccagaa 240
actagctttg caaacagtct tttcagatgt gtacattttg tgtatttgag gcatataata 300

tatatatttt cctccatgtt caccc 325

<210> 316
<211> 275
<212> DNA
<213> Homo sapiens

<400> 316
acgccatctc caaatacggt cacattgggg gttagtactt caacatatga atctgaagga 60
gagacacaat tcagtcctta acacagtgct ttatggattg tatctgcatc ttccatctta 120
tcaccaccca aatccagcac ctgaattggt gagtgttgcc agtgagaggc caagagccag 180
aagagcctgc ttctgcttgc agaggatgca cagttgtaat agttcgtttt catgctgctg 240
ataaagacat acccaggact gggtaattta caatc 275

<210> 317
<211> 352
<212> DNA
<213> Homo sapiens

<400> 317
gttcgtgaat gactgtggtn tcanantgac tgccaatgnc gactcctgat accataaaag 60
gaaagactcc tgtctgaagg atgtgccttt atcccagaca ctgacaaaca cctttgccaa 120
gagagttcag aaacgactgc aaaccccaac ccaagcaact ggactctgga aaacagctca 180
tgaaatctca gcatctgcct tgtctggtga gcctcgtagg gcactcacct ctattacgga 240
ggcttgatgg cagcggcttg gtttgaactc tgtattactt atctattgct gcataagcga 300
attaccccaa agcttagccc gcttaaaaca acacgcattt attatattca ac 352

<210> 318
<211> 243
<212> DNA
<213> Homo sapiens

<400> 318
tcacaacatg ggggtttggg ttggttttgg gatgggcaca cttntgcccc tgggacaatg 60
ggaatggtgg ntttacccag gcnttnnggg anaanangtg ggnaattcna ccccctngga 120
tgctnacaaa ccntggcaaa tcttancatt ttcccctnat tgaaaccggn tgccccttnc 180
cttantaact gcccttggac ttacctcacc attttgtgtg gccttaaatn aagaatttgg 240
ggg 243

<210> 319
<211> 476
<212> DNA
<213> Homo sapiens

<400> 319
actcagagaa gaatggaggc agaggctgga gaggaggctg aggatgctgg acaaccctgt 60
tgagaaggaa aagccggcac acaccgcgga ctgagctctg cctgcctcac cgacttcaaa 120
gatagcaagc gaccactttt ctaggggaaa aaaactaaca ctcaagttgt gctgatttac 180
taaacaggac gctctctatt tgtgcttcca tttgctaggg gatttacatg tgaaacctcc 240
cccagtgcta atgggagtta ttatcctgct caatcccctc cgcacagagg acaggatgac 300
cgcaagtggg ataggacgct tgggctattt aataaaagaa ctctttggaat taacacttct 360
tcanggctca cagacccatg tagcctagta tatttccaca tttccttgtc attttgaaat 420
ggttcaagtc ttgagacatt tgaagngttt tcttctaagc ttaccgaggg caatgg 476

<210> 320
<211> 66
<212> DNA
<213> Homo sapiens

<400> 320
aggaatcaaa agaaggagga agaatagaat gatttggagg aaaagaagga gaaagtagag 60
gagttg 66

<210> 321
<211> 226
<212> DNA
<213> Homo sapiens

<400> 321
ggtggcccgg cctccctgtt ccatcttctg agaggagcta tacccatttt gcaccctgaa 60
cctccaaact cagaagtctc tgaggagccc tgaataggag aaaatgtggc tgaaaatgaa 120
gtggaaaatc agtgtgataa ccaaatcaag atcacgcctc gctgggaccc tgtcacacta 180
aagcttccag agcatagtcg tttttaaaat ctgtaatagt acctgg 226

<210> 322
<211> 465
<212> DNA
<213> Homo sapiens

<400> 322
gaagccaagt gggaagatcc ttgctggttt ctccctctga ggaagaagga aaatgccatg 60
actcccacta tggcctctct tggaaccata ttttgaggta ccctacttcc ttcttgagtg 120
tcagcagagc aactgtggga ctggcatgag atttggtcat ttctaggaga gcgaatgcct 180
tttgcctctt tgatgagaaa actagacgag acattgttta gaaattcttg agctcagact 240
ttngcattat gacaacgtgc attcaaatct gccccagcca cttgcgagct gggacctaaa 300
gccgtgagct tctggttgtt tatctataac aagcggatcc cagtacctac ctcataaggc 360
tgntgngagg gattaaaata aaatgcatct atcagccagc ttgcaggtct gcacttaaca 420
ggggctcang tgcaatacct tgataagttt tgatagtttg ggata 465

<210> 323
<211> 303
<212> DNA
<213> Homo sapiens

<400> 323
cnaacctgnt angtntcatc tnatncaant gtggcaaccn ntnccttgnc cannngctgg 60
agctgacact ttctcaactt cacctggatg gacactgaag tccaggatgg gatgctgcta 120
cctgcagctg ccatctccct gccaatttaa ggatgaagcc aatgcccagg atggcagagc 180
tgagagctgg aaggaagcca ggtcctcgct gacattgttg acacactgca tcagccatct 240
ctcagcctcc cacctctaga tttcctgtga cttgggaaaa taaatttctg tatttgtaaa 300
gct 303

<210> 324
<211> 458
<212> DNA
<213> Homo sapiens

<400> 324
aatcaagaaa acaattcaat aagaatccat tttccttggt aacaggacac aattgaaaac 60
actggttatt taaccaaagc ttcatctgaa atggcatatt ttacgggata tgacgagact 120
gctttgagga atttaagtgg accttataaa gttgataaag agccccttag aaagactggc 180
ctagtacctc atntacttgg ttcccttagg agcctaggan cctnaanatn ttnggggacc 240
tcaagaagag agaaattcac tcatttatg cacatntnac nggcatagtc tanggggaa 300
tcntnggntg gggttccccg ntttnaaagn gtttttaaaa ccaanttnng gggtnntttn 360
taaacatttc ncccnaagnn caccttttaaa acccttttg aacnctttt ttttttttgt 420
ntttgcgcna aaatccgggn cccngggaaa aactaaaa 458

<210> 325
<211> 212
<212> DNA
<213> Homo sapiens

<400> 325
gagnnactgc tcaaacaaga acacaaaaat ntntnangat cctacnacag ngggttggnc 60
ncagtgcacg ctntgtatac ctatcagaca aaagaaaatg tcaagcaagt anaacagaga 120

cttagctgtg acagctaaaa natttataaa gtcatgcttc ccatcnaacc tatctggact 180
tatcaacagn atgcntccag cagttattcc cc 212

<210> 326
<211> 483
<212> DNA
<213> Homo sapiens

<400> 326
gtgtaggtct tgcctttcca gggataagtg gccacatagt tcgccgtgtt ccccgcagtt 60
attccagtac atgttttata cttttggtat gtttgttgat cacggtgatg gtgattgctc 120
tcaacacaat gtctacttct cctcgacggt caaggaggga aatagacaga gcccagaggt 180
ggccagccat ggttcctcaa gacctgccaa gaagagtgca ggccaccaga gtcttgcag 240
gtataattga ttaaagatct caagatgaag tcatcctaga tttaaatcat ccacatggag 300
ctgccttcaa aggcacagct gcaggcgagg gtacatttct aaatcccang actagtggcc 360
ttgttagaaa anaanaaccc ggggngaccc ccngagaaag gagatgtgaa gatggaggca 420
gagactggag tgatacagct ccaagccaag gatcaccagc catttcaaga agctaggcaa 480
gaa 483

<210> 327
<211> 272
<212> DNA
<213> Homo sapiens

<400> 327
agatgcagtt ttgccatgtt gcccaaactg gtctcgaact cctgagctca aagcaatttg 60
cccgccttgg cctcccaagc tggaatgaca gacgtgagcc actgcacccc gccaacattg 120
gcattctctg ctgcctttctc tggactgagg aacttcactc aacaactggg ctcacagccc 180
tttttccaca gagattttgt ggaatagcct ttttgtctca tgcctgcttt tcatttattt 240
gcttgtttga gataaattaa aagcagaaaa tg 272

<210> 328
<211> 450
<212> DNA
<213> Homo sapiens

<400> 328
ntatgacaac aaaaccaccn tggggcccaa acctggaagc cgncngctat ggaggaccct 60
ggaagcangc anagaaaggt ttggagtttt cantgcgatg acaccagcgt gcctgcggaa 120
gnggntgtgt ntactnttgc ctccttnccc acccaattcc gtcccaggag cccagggatg 180
gaggcccaag anacggatnc cacaggagcc agcacccact ccaccccagg agctcagcaa 240
acatccacag agtgaacatt ccaagcaaca tagtccagga gccacgttcc agccatgggg 300
cctctgcact gctgtcctct tcacatggcc tgcccttccc ccagaaagag agaagaggcc 360
ctctctggtt gtcccatcaa aactccaccc ttctctcacc ctcctcccag ctgtatccct 420
tctctgcagc cctaacatgc attccacttt 450

<210> 329
<211> 479
<212> DNA
<213> Homo sapiens

<400> 329
ggtgtgggca cacacactct ctgaacagca gaacttctgt ctgagagtag aagctgaaga 60
gcagaagaga cactatggga atcaggaaag aggaggtgat ctgggccagc agttgaagca 120
cattgaaacg aagaagaagg ctgacttctc aggagctgcc tggatgctgg cctcctgggg 180
aactggaact ccagtttgaa ctgaaattcc ctgtatactt gtcaggaaca tccactggac 240
tgtgggttcc ttggtacaaa aactaagtat ccccatgcct gccacagtgc ctggagcaga 300
acagacactc aaatatttaa taacgtatga ctgattgtgt attacccgcg gcatcaatag 360
aagacacaca ggggggngga ggataaattt gggttaaaaa anaaggctaa atctgntggt 420
gntgcttcac atganaatga nagtctttcg gtttatggtg gctccccggc caaaacacc 479

<210> 330

<211> 171
<212> DNA
<213> Homo sapiens

<400> 330
gaattcatga cactgaagct acccaacttc taccatgcct ataacatgat caccctagga 60
agtggcagag taacccgagg gaagaagcct ggatacctga atgactatat gaaacacagn 120
tgccttaata ccctcgatca ctcactacgg aactctgtaa taaagtatat t 171

<210> 331
<211> 251
<212> DNA
<213> Homo sapiens

<400> 331
atgctatcta tacttatgtt aagcatcttc agagacacca tggatgatct tcattctgaa 60
tcccaggaag aattctggaa agcaatcacc tacctcttga tattttctcc gtcagatatt 120
acctaaagat ctttttggga cctggagaaa agggaaggta gaactgattg atacttctta 180
tttatataga attaaaagaa tatgaaaagt ttagataaag gagcataaat aaaaaccttc 240
tactggcaaa c 251

<210> 332
<211> 446
<212> DNA
<213> Homo sapiens

<400> 332
gttgtctgcc aacgctaact ggccagctct gacaggaggt gcgtggccca ggaggagcca 60
tcaggccagt tctctgggat actgctgtgt ctccagctct gcagtttgct ctgcgtcact 120
cagcggcaga cggagaggca gacacgagcc ccttgtgagc cctcctcctt accgtcatct 180
cacaatgctc tgaaataagg aggcaaatgg ctgaggtccc ctcagttgaa gatgtgattg 240
agttctatct accagaagca tatgcctcct ggaagcctgg ttctaacacc tctcacaaaa 300
tccttcaagc actttttttt gtttccaaggt ttgcttatgg gggacccnaa ggaaaggggct 360
tnanancccct aaagatttgc tgagtcatat gaggggccag caaacttttc ctgtaaaggg 420
tcagataata aacattttaa gctttg 446

<210> 333
<211> 498
<212> DNA
<213> Homo sapiens

<400> 333
gtgttgatca tgaaacattt tcaaccaaaa atagtagagc caaatttgag cattgccaac 60
ctccacccac ctcccttcat cacatggatt tgttccaaac aacttctggc ccttcaagca 120
aggaaacact ccttcaaaag atgaacactt gccatcacta acattgtgcc acaggctctt 180
aagacaattt caaatggaaa tgcaacgaag ttttgctaat ggtagcatca ctgaaataag 240
tgtagtgtct caaaagactc ctatgtgatg gtgaagaatt aagtgtgtat gtttaggcac 300
aagttttatt tttcaaagaa tatttcatct tgctatttgn cgaatgaaat cttaaggaat 360
aaaaagngnc ttaagttttt ccaaattgca aaaaggaatt accatcttcc cactgactcc 420
atgaatgcca aagtcactga aaactaagct taatgactgt tgaatcaatt tccaaagatg 480
taaaattctg ctttaata 498

<210> 334
<211> 345
<212> DNA
<213> Homo sapiens

<400> 334
gcaaaataca tgggaaaaac aaaacaaaac agtgaaccaa gaactcaagg gagaatcttt 60
tgagctcatt ttctgggtga atgcttccct cttacccgac caccagaaca gaggagcttc 120
caggaagtta gagaattgaa aaatagagaa aaagaatgag tcacaagagg atcttatcat 180
ctgactaagt gggagactgg ataaaagcct tgtaaaatca ttgcagctta tatacatgtg 240

tatggttatc aagtagcatt ctatttctca aattaagcat ataccgcant tattttgtga 300
gactataaan ttcttctaga aagaaataaa gaacattaaa attct 345

<210> 335
<211> 297
<212> DNA
<213> Homo sapiens

<400> 335
aggacttgct cagaacaagg gaagaagatg actatgcagc tgctcggtaa cagcgtctag 60
tcacactctg agatactgag gtcagcaaga acagaggatg cacactatgt cccatcttgc 120
ctttctgccc agaaagtctc agttactgga aaagcttcag aaatatttac caaaaaatcc 180
atttgaaatc ctgaaattct acttctcaga aaaacagtat tactcttgtc tagaaataac 240
attcaggcct caaagtgcta tactgtcatt acttctaaaa ataaactgag caaatcc 297

<210> 336
<211> 175
<212> DNA
<213> Homo sapiens

<400> 336
tattgtttct aaagaaacta tgaagcaatt caaccagagg agaacaacta ctgtgggact 60
gcagatgatc ttagcctgga agctgcataa ccctcctacc agatcaaatc attcagcatc 120
catcttaaat gagaaattta agtaactaaa aataataaat ataaataatt aaaat 175

<210> 337
<211> 496
<212> DNA
<213> Homo sapiens

<400> 337
attcaagaga gtgccaaagg aaacaacagg acagaaggag acatgaggaa gagatgggac 60
agacagcact caaccctgag cagacgtgag gggcaaaaga aaaggcaaca ttaaggaccc 120
attcaagttt caagtctcag cgtcccagag gatggtgagg atacagcaaa aatggagagt 180
gcaaaaggag aaaggcagtt gaatgtgaag ataacggggt cttcggggcc tacctactaa 240
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ggaaaaaaat ggctgcctgg aaagttcata taccagcagc aaaaagaaaa gcnnaatggg 360
attaaaaaat nttaaaagcc cttcacnagg aggttaagtt ntggcgggtg tgcccatcag 420
agaccagcag agacaactgg ctctccggcc tgagttcgcc tacatcagaa ctagcacatc 480
tctctgtcta atttct 496

<210> 338
<211> 371
<212> DNA
<213> Homo sapiens

<400> 338
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ctcattttcc tccttgccat gagctgcatg tccccatgat tcggggcagc ccgcctaggt 120
gcctgttcct ggctatcaga agagcacagt gaagtcctcc tgcccctgag aagatcgaag 180
actctgctgt ggtcaaggtt ccttctccag ccatatgtgt tgtctaggat tagacttttc 240
aaacagtggc caggccttct gaggtcacat gtagcagtaa aagcaagctg tggccaaaaa 300
aaaaaaggnc ngnggggncn attnannttg gacttaancn gggngnactt nntnaaaagg 360
gggggactcc c 371

<210> 339
<211> 479
<212> DNA
<213> Homo sapiens

<400> 339
actgaggatc ttctgaattg gcggcctcta catatgcttc tgctaaggag catgtattca 60

ctcaacaagc attttaaacc cccagcaagg cacaagctac aagggttaca agagacacaa 120
gaagagatga ggtggctcct gcttcccaaa gagtgtggtc cagggaaagg aataggcctg 180
gacttctcat aacctggaac atcttttctc gaggccaaag aggtgatccc aagtgagagg 240
ccaaatccaa ggaccctgcc tgcccgatgg gtgctcctct gctgagcagc caaaggcagt 300
gccacgaggc ttcatctacc tccaatagtc acggagtctc tccatgtgcc nnttgggttt 360
nntgcnttgt tttcccagga aagccttnct tgacctttca gatcaagtca catccacgta 420
ccatgaacat tcacaccctg tacctctctt ttcacagcac ttatcccaag agaaactcc 479

<210> 340
<211> 481
<212> DNA
<213> Homo sapiens

<400> 340
cagagtgtgg gaccaaggac aaattacaga agcacagcag agaaggttgc ccggttcccc 60
gtttgcctat gaagttatgt agtgagcaaa taagaggaca ctggagcaca gcgctgctta 120
gagccgaggc tcagtaaact tttgttcact gatgaatgaa tgtattaagc tgaccagctc 180
aatttgattc ataaagaaat agccttaggg cttttctgag gaagaacaca acatactttc 240
aatccaactt tttaaaaaat aaaacatgat tacacactcc taaataaata ttttcagaaa 300
gtttgcctat atgtcaaaga tttctaggat ttggaagcca gtatgttcgc aagttgtgag 360
gacatctgng ttatttctcaa cacttccttg gcaaaacnan ngngtcctta cctgaaagcc 420
tgaaacaata taaaatgcaa agctgacatc cccctgcctc ggcaactgca ctttcaccca 480
g 481

<210> 341
<211> 306
<212> DNA
<213> Homo sapiens

<400> 341
aaggaaagat ggaaaagagg agttatcatt tctttctcaa gatcctggcc ccatgagcct 60
cagtgtagcc ctagttcctg ggatcagcac caacaggcag ggaggagagg ctctggcgcc 120
ctgcagacag caccaggttc ttggcatcag gagctggata cagagtccct gataatccca 180
gccacagaat atttcaaact caccgacatg tcctctaaat atcagatatg aaaaggcttc 240
cactcttgca cctgtcttgc tattatttta cagatgtgtt ctaaaagcta taaagacgga 300
aatcac 306

<210> 342
<211> 471
<212> DNA
<213> Homo sapiens

<400> 342
ataatacaga catgtacccc accacacaca atgtaaactg caaaagcaaa aaaccgagat 60
gcctcgtcca cagttcaacc ctctgcgaac agagccatcc tggataaaag ggctgctgtc. 120
atgattgcca taaactgagt ggcctgaaac aacagagtca gaaatcaagg catctgcagg 180
gccatgctgt ctccgaaggc tcggaatatg gacccctcct tgcctcctcc tagactctgg 240
gcaggctgca gatccagaaa gccgaagctg cagcaagtcg gaaggcgcgc cgcaggagga 300
gttccttcct caggagactg cagtctttgc tcttacggnc tttgaaaaan atggnatnaa 360
ncccccnacn ctatggaggg taacccgctg cattcaaagt ctacagattt aactattaat 420
catatctaaa aaacagcctc acagaaacac cagactggtg tttgaacaaa a 471

<210> 343
<211> 463
<212> DNA
<213> Homo sapiens

<400> 343
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gagctggctg tgtgacttgc tttggccaaa aagactttag caaataagat ataagcacaa 120
gcagaggttt gaaaagtgct ggttcgctgg ggcttactgt attactgctc ttgaaatgct 180
gagatgacca tgtgaatgaa tccaaggaag cctcctggaa gatgagaatg ctgcatagaa 240

gaaaacagag gtctccagct gacagcctgc caaacactag aaatgtgaat gaggccattc 300
tggatcatct tgtcaccagc tgacctccca gctgactatc agtgcatgag caaacccaga 360
aaagatgagc tgagccagtc cagtgtaaaa aaaatggccc agccanccca cagaataatg 420
agctgaataa aanggttgtt ttaagccaaa aaaaaaagg gcc 463

<210> 344
<211> 149
<212> DNA
<213> Homo sapiens

<400> 344
gagtggaagc agcctgaggc cctcatccaa tgcagatgtc tgtgccgtgc gtcttgtcca 60
gcctgcagaa ccatgagcca aataaacctc ttttcactac ccaaaaaaaa aaaggncagn 120
gnggccaatt cagnttggac ttaaccagg 149

<210> 345
<211> 407
<212> DNA
<213> Homo sapiens

<400> 345
tatatgaaga aatctggcct cccacagaga cggatttgga aacaagagga ctacacagac 60
cctctgacag tctcttgggg gacacaatgg cttgccaagg gatccttgat acacacttcg 120
agaaccactt gcatagacca tcaccatcat cctggaaggt tttttcaaaa aagaccacta 180
ctctnacttt cttnaanaat aacattgcct tttcttgatc ttnatggatg gggaatcatn 240
antgacntgc tnntttgaaa taaaggacnt ttgaaaatan aaacntggac ctatgaanat 300
atnaatcgga tgaagattct gaagngccct gatgntacta tttatggnct gnttaaatat 360
tccaacttaa tgggaaggcc ctnggggggg gatttggcca ccctttgg 407

<210> 346
<211> 363
<212> DNA
<213> Homo sapiens

<400> 346
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gtgaacatca acactggaaa ctcaagagtg tgttaaacag agaaaattaa tagaaaccag 120
gaaacactta aggtntattt gaagtttgtt gtcttgaatt gatgtattaa ttaactctgg 180
aatcaattta ctgtatttgg tgaacccagc tttcagtgga gttcttctta attttcgcct 240
actgttctac ttgttccaaa tgtgtgtatc atgtattttt tcttttagat ttttctacct 300
aattagcttt gattctgtca tcaggattga ttttggctaa aataaaacac atatatgtct 360
ttt 363

<210> 347
<211> 383
<212> DNA
<213> Homo sapiens

<400> 347
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aggagccgag accatctggg gtgggaccga ccaagagttt gaggtgtcca gggggtgacn 120
gtgaagatga cctatcgcag agggtccctt ctcattcacg ctctgaagtc tgcacagggg 180
caggggctac cgtgctccat tcagtttggc ctctgttgta tcagccagag gccagcagaa 240
ctctatggtc actcccccgt gtcacggaca atttgccacc tccaccggca gcccagggct 300
ctgcctgaat attctcgcct gatcgtagga ttgtggggag ggatattctc attgatctct 360
aaagaaaata ttggtcgctt ttt 383

<210> 348
<211> 479
<212> DNA
<213> Homo sapiens

<400> 348
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gccacatgaa ggtgttctgg ccagcagtgc cagctgaatc tcagttgcaa gccagcatga 120
ccaccagaca gggaagtgag caaaccttca acggaggcaa gccccagcct tcaaaccacc 180
ccagccgatg catggggcaa ggacgagcca ccactggcaa atgtgcccaa actgcaggtt 240
caggaggaaa ataaatgatg gtggtgtttc cagtcattaa gttttatggt ggtttttaag 300
gcaaccaaag acaactaaga acatttactc tggccaataa aaaaatgaat gaaagtgatg 360
tgtcacttcc atgtggaaag ngttcattcg ccagtagtta agacattgga agcaagcttt 420
tccttcttgg tgcaccaatt angaaaagaa gtggtgttgg gggatgtgcc ctccttcat 479

<210> 349
<211> 614
<212> DNA
<213> Homo sapiens

<400> 349
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gcggaagaga cggcntttcc accccgggac cttaccagaa aacccgcaca ccccagncac 120
aattggcttc cttcattcaa gccnagaaaa agggactccn acttttcacc accaggggan 180
gccccccttt cttggtggct tgggccaant tgcaaaaagg cctngtttca ttgggcattn 240
ccacaagggt ngggggggaa nttgggnccc ccaacccttc ctttcttang cacctttnan 300
aagnggttnc cttnttgttg ggcaagnaac aacccaattg gcnttaaggg ttttcntctt 360
ttttnccaaa cttnccttgt ttngggtctt ggggcnnaag gtggnaccgg aatcaattct 420
tttccacttt gccatttaaa ttnaagtnaa gttcaacccc ngaaacaatt tccttaatac 480
cttgggggcc cccccaaatt tnctttttttt aaaanaaacc aaagtttggg cctntccccc 540
ccacttgggg aaatttattt tctaaaatat tngggaacnt tagaaattaa aaanttggaa 600
gaaactttgg cccc 614

<210> 350
<211> 380
<212> DNA
<213> Homo sapiens

<400> 350
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ggggttggag agcccgggat tctgattaaa catggaatct gagaactggc agaaagcctg 120
gaactgatgg aagagagggc tctagggcct ccatactaaa tggtgaacta ggaactataa 180
aagagataat gtggtgaaga gcttcagcca tcaagttatt ctaaaaatga agtagggcat 240
tttatatgtg gagagaaggg cactgattat tatctgacta ttgctaatat gtcccataga 300
acttatttgg aataatttttt tactattaat ttgaacaaca gcagtgagac tctttatatg 360
tataataaag ctaattttac 380

<210> 351
<211> 373
<212> DNA
<213> Homo sapiens

<400> 351
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gccacagagg gaaagccgcc ttgagtatgg agcaagactt cctcagacag gtctcatttg 120
tgtcttccct tccagcagga ggaagacagc acctgcccag agtagtttta gagggcactg 180
cactaaagaa ggagaactgc aggggaagat cgtgccctaa tggatgaaac atttcccaaa 240
tggcctggct atctggagag atgaggactt gctcattagt agaagtttcc aggcaaagcc 300
tggataagca tttgctgcag gggtggggga aggtgaaggt tganangana nctctaagat 360
ttctttgcct tgg 373

<210> 352
<211> 405
<212> DNA
<213> Homo sapiens

<400> 352

gctataaaga cgccttgaat cctcctccac gatacccgcc ccactatttg ttggcacagc 60
tacgatgctg cttatggatt gttttcactc ctaaagacag tggcgcaagg caaggtgacc 120
tggagcgagg ccatcctgag tgcccaccca gcgtcccagg agcctgttgg aatttggaag 180
gacatttgcc tctgtttata aagactggct tttgctgaa agccagggtc tcaaaaattt 240
tgttttatta atagaagcta aaccccaaac atttggctct ttttcattcc atttcccctt 300
tcacaatctt aactattccc aagacaatgg atacctctgc ctgtatcaag ggcngattgt 360
caataanaaa gtcaacagga aataaacntt nttttttca aaatt 405

<210> 353
<211> 464
<212> DNA
<213> Homo sapiens

<400> 353
ctgatttaag ttanttccng gggnccnaaa cctngnaaag gtttttnatt agggcagcaa 60
agggaaccgg ggaaccactg angaggagca gcagaaaact tcacagcttc tttgggtggg 120
cagcagactt cagatttact ggaagccaag aaaggggaag acagcagcag gagggcttga 180
ccagctagct aaataagtta agccatggaa agaagcagaa gaaggaagct caagaaatct 240
cagcaacaaa cactcatgga ctttttcta aaaatggaaa tttaaaactt tctcgaccat 300
gacccacaag aaatacattt tacacgttgc atccaggaca tagcaatatg cctgtgagcc 360
actttgtggg tgaagggttt ncatggtgag cttgtttaag ggaacatggc ccccnggggt 420
nctcctttg gagattcccc ctggatttac tggatcaaag tctt 464

<210> 354
<211> 446
<212> DNA
<213> Homo sapiens

<400> 354
ggaaatgcca caagactatg gccgtgcaac atttccgcag tgctcctcgc tacaaagaca 60
ttcccctaag gctggtgggc aactcaacac tcagctcagt acgtggtcag ctcgtcctcc 120
ataggagcct tatgccttgg tgaggagatc tctgaagaaa ttgctgatga aagtccaaca 180
ggctcttcca gtttgtctgg tcggtcacat ttgctgaaac ctggaggaat tgttagtgga 240
agctcaacag gcctgactca gtctgactgt ccattcttct ggaagctgca gagaaaagaa 300
acctggaaac cctatatgct gacaaaaagg gacacaattg gatatgatgg ttattttacc 360
aaggttttga aatgtcgtgc tttcaaatat aaacagactg ctttaangga tcnaaagtgg 420
ccttttaaag ccaataaaag ccctgc 446

<210> 355
<211> 446
<212> DNA
<213> Homo sapiens

<400> 355
cagcccagac gtggtcaaca agaacactga gcagaaaaac aaccttgagg atgaaaacag 60
ggatgttctc agttgaagcc cacactagaa gagctattta aacagcacca aagtgctggg 120
attacaggtg tgaaccgctg tgcctgaccc agtgtttcta aaatatctac aaaaacagtt 180
tggagttagt cctaggcaat gctttgctgg aaatgggatg tgtgatggac cattctaagg 240
gagctgaact ggctgctgtg aagacatcag gaacccaagt gagactgtgg tacgtaagtc 300
aggaagaagg cacttgcctg gttttgaaaa catgtcctgg ggatggntag tgcctncagt 360
tcacaaaaaa agcaagctgc cttgttaggg nanggannca accanttgaa aacacctcca 420
ntactgccan tanaaacagt tgattt 446

<210> 356
<211> 450
<212> DNA
<213> Homo sapiens

<400> 356
aggctgagaa gtccaagatc gagggatctg gcagcagatg agggcctttt tgttgcacca 60
gcccgtggca gagggtggaa gggcaagagg acaagaaaga ataataaatc aaacttacag 120
cctcaagctc ttttataacc agcatcaatc cattcatgag gatggaacac tcatgaccta 180

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aacacctccc tttaggctcc accttccaac atttgttaaa ttggggatta agtttctaac      240
acatgatttt gggcgggata cattcagatc agaccaaaag ggcaaaggga ttttgtatac      300
acagagaaga agttgatgtg aagatggagc agagagccgt ttgaagatgc tagccttgcg      360
actggagtca tatggctaca atccaatgga tgctggtaac cnccaaaana tgganggngc      420
ccggacnaaa attcncncct ggaacctcca                                       450
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<210> 357
<211> 460
<212> DNA
<213> Homo sapiens

<400> 357

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gtccttccag aagagcactc cccatcaacc cgcgggcagc tgaattccca cctcagactc       60
tgctccaagg gcgccgtgtc tacggaggcg acgctgagga tggcttatca ggttgggtca      120
ctcaccccac cacgaggacc tgaccttaaa ttctcggtgc atcctaagtg tgacccagag      180
accgcctgcg tcagaagcac ctagaatgct gtggaagcac cttcaatgca gattcctggg      240
cccaaccctg gttccactga atcggggtca gctggtgggc ccaggaattg gcattttcaa      300
cagcttccaa ttgtacacca gaatactcaa gcttgtgact cccctgctca ctgntttctt      360
catcctttct cacttcctgc tgagtacata tgnattttac tacttttaaa aganactttt      420
accaataaag gccggcnttg aaggggaaaa aaaaaagcca                            460
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<210> 358
<211> 419
<212> DNA
<213> Homo sapiens

<400> 358

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gaccgcaatg ctcctacgat gatcctgtaa cagaggtatc ggacaccaac cntgggannc       60
ctccttcaaa ttatgggaca tcaccaacaa tcaatcacta agagaagaaa taatttagaa      120
gaagaattca tttttggtta ctcaaatata acccaattta aaggagactg ttatttctct      180
tctctagtaa gctacagaca ggatctgctc cctttaataa gatgcttggt taataacatt      240
tatttacaga gtaaaatttt ctctttattt ccctccacac taaaatattt acataaactc      300
aaaccactta tgttgcctat tccaaccagt ttcttgtcag agtgagtagg aaaattcttc      360
attaaatgtc attgcctttg gggnaaacag aacataaatt aaaaaccccg ctttattta       419
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<210> 359
<211> 455
<212> DNA
<213> Homo sapiens

<400> 359

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gccaagagat gcaaaggatt aatcatgaac ccagttgccc agaggtggaa aaaaaaaatc       60
tgttgtggta gactgaagaa gcnagaagtt atatgaacac caagaggccg gcaacatgag      120
tgtggcctga gtctgacgcc ttcgcccacc ctcttccaga tcacctgatc cgaaagaagt      180
tacgaaaata gctcanaatc tgggcctgcc tggaagagac ataaagattc atttacatgg      240
gaaggtgact gctctgaata tccacagacg acgaatctat gctaatggtt cagtctccca      300
caaatctggg atttatataa ctggctccta cccttgttcc ttgccagcag aaatgcttga      360
attatcttaa ttccagaatg naaattattc ccattctgan ggcntcattt ttaagctggc      420
aaaggncatt tttttnacag gcctaaaaaa aaatt                                 455
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<210> 360
<211> 465
<212> DNA
<213> Homo sapiens

<400> 360

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atgatgtcag aagtggggtg caaagtanag gcttctgaca acccccggga gtactgagtg       60
aacaagcaag gtatctgcag aacccacttg tgtccaccga tctctcagag tgcctggaga      120
tcatggacaa cagaatgcag tgtgagggat gtcaagtcat ctgggaacaa cactttctta      180
agaattcatc tcaatttctg cgtttttttgg aaaggtcctt aattgtttgc tgcctctgca     240
agctagacat ctctttcagc aaatggagac ccagatggtg aggcaagaga aggaatgacc      300
aaattaatga aaatgttctt tcagcttgtt attgagcttg ntattctcct gaatgcttgc      360
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tctgcgactg ntatgctaac tgaccctgtg ggtaaaanga gaaaggaata tctcntttgg 420
ttaatttaaa aaatantaat aattgacaaa aaaaaaaggc ccccg 465

<210> 361
<211> 332
<212> DNA
<213> Homo sapiens

<400> 361
gctgtaggat gacgcatgat gcaagtctga agttgtatgt ggccatcttt gccaccacat 60
tcagaaagct tacctgagaa tgaagtcaac actggagaga aagagaaaga aagagggaga 120
acatatcaga atctctccac aatggcaaca aagatggtca ctagcaagtc caagcctcca 180
ttctctttaa aacttgcaat ccttgaggac aaagaaaaac gatctttttt tccaatatct 240
atgttacttc taaaagaagg nattaaggaa agcctgnatg aaatttcatt catnantcaa 300
gaccatactg gccttgaata aaatttataa gc 332

<210> 362
<211> 293
<212> DNA
<213> Homo sapiens

<400> 362
ggagatcggt tggaaagaca gtggactgat ccaagagccc agtcttgatc agcccagact 60
gaggggacct taagagatgg gaagactgac atttacaact tccccaactg gccgtgatga 120
tcttaagtac agccactgag gaagccaact taagaatctc ttcctgaccc tgctcagaat 180
tctatcatcc ttcttcctgc cccaaataaa attcccactt ccacaaaaaa aaaaggccan 240
cgnggccaat tcagcttgga cttaaccagg ntgaacttgt tcaaaagggg ggg 293

<210> 363
<211> 466
<212> DNA
<213> Homo sapiens

<400> 363
ttgtgcgtca ctgcaagact gcatggtaat gaagccaagg cactgtgggc caaaactctg 60
ctgcctgtga gaagagaagg gacagcggct tggagagaca gaacggcaaa accgctgctg 120
ctgctgcttc tgcttctgct gctgctgctg ctgctgctgc nttgcagct gattgagaca 180
ctatgttgag tctacaggat tctgtgtttt ttgaaattag cataaagtcc ttgttaaagt 240
cctggagcag cagctgaagc caagtaggct gcccaggcag tcagaagaac agagcaggtg 300
aagctgcaca gcatgcagtg gtgtgtcttc ttttggggcc aagcctgatg caacttacta 360
tttgccaacc cccggtcatc ttccttctga gtaaatggcn ccactatcct atgagtgatt 420
caagtaaaaa tgctcttcag cgccagtcag caaagtaaat aaatca 466

<210> 364
<211> 283
<212> DNA
<213> Homo sapiens

<400> 364
tcacgaacaa tctggatttc atgtcacaag aggaaacaga gtcatcactt caagtactgc 60
accaatcaag tctgttctgg taataatgtg aggcatgcct caagacctcg atacatgaaa 120
gcaattactg cagatgcctg gctgttggca ctgttcagct ttaatgtagc agtacagaaa 180
gttatgcctt ccacctgtga tgactgatcc tagaacctgc agacaatgag tctaagctga 240
atacaaacaa taattatcca agtaaagagc ccttgttcaa ttc 283

<210> 365
<211> 407
<212> DNA
<213> Homo sapiens

<400> 365
aaatgaagat ggcatatgga aaggcgattc ttatactcag aaggaaaagt tcccatggaa 60

gccatggatt cattcatgac aaagtgggtg gcctgtttgt ttgcttgaga ttggcaaaaa 120
tccaaaatgt ctgtgcacac tgctggtgag gctatggtaa aacaattaca tatttctggt 180
tggtgtgtcc ttgtgaagtg aaatttggca gtaagtaaca aaattactca tgcatttccc 240
acggatcagc atctccactt gacataaaat aaatgctaga gatacacatc tacaggtatg 300
aactacaagt tctgtagtat acaaggatac aggtaattta ttctgttgtc tatgatggca 360
taaacagctt aaagtgctta ttaataaggg gcctgggttt gttaaag 407

<210> 366
<211> 466
<212> DNA
<213> Homo sapiens

<400> 366
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ctgtactcac acctgagcag catctatgcc aagcctcagg ggcggctcca cccacactgg 120
gagagccgag ctccgagaaa gcatccctgc aagactgggc agttgcagac caaccgagct 180
cgagctactg tggccccct gcctatgact cctgtcccag gcagagcctc caagatgcca 240
gcagccagca aatcttcctc agatgccttc ttcctgcctt cagagtggga gaaggatccc 300
tcaaggccct aagtcaccag caccagagcc cagctgccca gcttaaccat attcatgctc 360
aggttcacat aatgggctat ttgnggtcaa gacttgcttt tttttcccn ggganccttt 420
tntgnggggag ggnttnattg ggaaaanaaa nagcctttcc ttgtcc 466

<210> 367
<211> 475
<212> DNA
<213> Homo sapiens

<400> 367
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aaaataagat gacaccctct tggaagattc ggaaaagtgt atcagacttc aagagccagc 120
tcagctacta cttcaagcta acctttcttg agacctcccc tttacctgct ttcatctgtg 180
ctgcccgttg acttaactga atcacctagt ggactgaatc tggccaaact ccagggccac 240
ctatcatgag cagccttgtt tgctggcaat ttgcagagtt gcaaggggta aaggactggc 300
tttgactatt cagtctttca gttcatcaca tcttgcctgg atgactgcag tggccactaa 360
gctggtcaca gagtgagctt tcttaaatgc aagtgtnaag gatngnnaaa ccctcaaggg 420
gctttnantt tttccaaggg ccctgtncct tggaggggca taccattgaa gggta 475

<210> 368
<211> 466
<212> DNA
<213> Homo sapiens

<400> 368
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ctgggccctg gaaatcaaat ggctttccca ccctcaagct tggcccagaa gggaaacccg 180
ggggaattac cagggccctt gaancccact ggcaggccca gcccaggtnt tggttaattt 240
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nggcaaactt ttggaattct tgtggcctcn cttggggaat gccaattccc ttcaaagcct 420
tgggcnccca aaaataaaag gtcttcccgc ttgattattt aaaacc 466

<210> 369
<211> 475
<212> DNA
<213> Homo sapiens

<400> 369
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ctgaagatat actaaggatt aaggcccagg ttcatctagt gtccccaggt gccaggcatt 120
gtgctgtgac tgtgatgtga aaaaagaggc caggacaact gggtctcatt cagtcagact 180
ggagtgcagt ggtgtgatca cagctcatgc agccttgacc ttccagactc aaacaatcct 240

ttcatgtagc tgggaccaca ggtgcatgcc accatgatca gtttatttttt aaatttttg 300
tagtgagcca ttgagtccag cataatcctt ctaatttagt tccttatctg aaaagcgagg 360
acattgtgac aatgatctca gaacactgtt gngaaaanta aantctnaan ataaagggtn 420
ggggcccaaa aggctttaat tggaagttgg cttaanctat aaaaaaaaaa gggta 475

<210> 370
<211> 387
<212> DNA
<213> Homo sapiens

<400> 370
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gttctcacct gcccttagtg gaaaccttct attcatctga tctatttttct tgtgggtgtc 120
agggcccaca tgtctccatc tccctttcca gctccaagat atctgttatg ggctgcattg 180
tatctccaca aaattcatat gttgaagctg atatgatttg gacctgtgtt cctgcccaaa 240
tcccatgtca aacgccatgt gatgtgtgct ttccctttgc cttctgcatg attgaaagtt 300
tcctgaggcc tccccagaac caagaagatg ccgcatgctt cctgacagtc ttcaaaacga 360
tgtgtcaatt aaatctcttc tctttac 387

<210> 371
<211> 462
<212> DNA
<213> Homo sapiens

<400> 371
gctggagtgc cgnggcacga tcttaactta ntngnaccnt tngcntccng ggttnaacca 60
nttttcctgt ctcagcttcc ccagtagctg gggattacag cgccctctgg taggcattgc 120
agagagaaga atgcaaatta aataagaaaa gcccctctgcc cttcaggagc ttttggtgaa 180
gatctctttt ttaaaaagct gcaagactgc tgcccgaagt gggacacaca acctaaataa 240
gggcgagaac cggcaaggac ggcccagcca cgtggaaccg cctcgcaact ttggcgagca 300
acttgagatc ttctagagac ccaggagtat gttgcttcta cctcagactg gggagagggg 360
agcttcccca aaccattggn gggagatgaa natntcaacc anccgaattc ctgttcacga 420
ccaacctgtt gtgagctctt ctgggggatc aacaatggct ga 462

<210> 372
<211> 263
<212> DNA
<213> Homo sapiens

<400> 372
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naggccagnc ccgggggttc acccntgtan tccagcact ttggaaggcc aaagcaggtg 120
gatcactgga ggctactttt tgttccttca atgcctattc attcgtctcc tctactcccc 180
gcttcccctt ccttcataca ccaactcaga gttcgaggca cctgcccatt tccttccaaa 240
taaaactgta aagaggttac aat 263

<210> 373
<211> 230
<212> DNA
<213> Homo sapiens

<400> 373
gaagtcaagt tgattacttg gcatcagccc ttcatcacag atactactga aataaaaaac 60
caagggaatg tgaaaaaaac ggaaggacac tgaagcccgt ggggaaataa tgaagtataa 120
gtgcttcaga gagcagcaag aaatggaata atatttcttc tgtgaggacc tcagtaataa 180
caacccatga gtgatgggac ttattgcaaa tggcaagagt gctgttggag 230

<210> 374
<211> 338
<212> DNA
<213> Homo sapiens

<400> 374
ncatngtnng ggagttgntg naaccactgn ctgactcttc atancaccnc gcttttncct 60
tggtcctcna cactgggtgg ggagccctac nttccatgaa gncttggcaa acngggtgga 120
tcggnntctg cntatcacag ccatacaatg actcttcagg aggaaatacc agcctagacc 180
tgctcagggc ttaccaaacn gtgacnatag gtgaggtgna gccagactag actnacacca 240
nttcggnatg atctgacgga anggccggca gaccctatat cctcagatgt gtccccatcc 300
acctggcaca tgtctggaac ttcncattac agaggggg 338

<210> 375
<211> 412
<212> DNA
<213> Homo sapiens

<400> 375
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atggctgtaa cttccttggt gccgaggact ccctgctcag ttcctactta cagtatctga 120
gtcacttaac taaatgcaat cggcccagct gcaggcacca ctgctcgggc cactataaga 180
accagcccct gagcttccgg acaggaaaca gcatctgcat ttccagactg tagcagctca 240
tcatgccagg ctccacaggc aagaatcaag cagatggaag ctacagagga aacaaacagg 300
gttccctgaa atcagcagct ggggagaatt tatcttacaa gggtggaatt cttgattctt 360
tcattacatg tcctcttgca gcagcagcaa aagtaataaa aaataagagc cc 412

<210> 376
<211> 416
<212> DNA
<213> Homo sapiens

<400> 376
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agaagactct ctcaagaaca actgtcttgg attcccacag ctttcccctt tctgtggtca 120
ccactcagga ctccctaccc tgccccacaa gcctgcagat tctgagatga cctggaagga 180
acggaacagg aaggcgtgag ctttggcacc agtttaacgt agaactgtac gggccaaaca 240
cagggccttt gattatagaa aaaaataggc ccattgtctt ggtgggtgga accaaagcat 300
agcagcatct aagaaaccag tttctttgtg tccagtgatg agggcttagc cctaaaatat 360
tanggtgggg agggaggagg ggtgaaannng naaacatact ttaataaaat agatta 416

<210> 377
<211> 253
<212> DNA
<213> Homo sapiens

<400> 377
tcaacagtca taacttttg aggacacatg tttattgctg ctgctggggg cagctgctct 60
tgtacccact ttcaaatggg ctgtggaaga gacaaagctc atctggctgc tggggcagtg 120
gcatcctcat gcaagctggt ctactggtgg ctgcccctgt gacctgcttc tgaatggcca 180
ggcaggaaaa gtctcccact gtgttgcatt taaagaaaag aaaaagatga attaagtaaa 240
aagctctgca aac 253

<210> 378
<211> 303
<212> DNA
<213> Homo sapiens

<400> 378
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agaagccctg gtctttgtct ccacaaatgc tgaaactgac agtgtttctc ccagagtcca 120
agtctccatt agccaagcca agagcagagg aaatgttctc cactggagga aagaagaact 180
gtcgacacca gaaaatttcc tgctggaatt ctgccaaaga atagctggcc gtcctaggga 240
ggtccatcat tacggaactt tgctgtttgt aaatttaata aacgactcac atctgcttat 300
aat 303

<210> 379

<211> 382
<212> DNA
<213> Homo sapiens

<400> 379
gtgtggagca gagaaaaggc tatacccact gatgaacagg gatccacacc tggggaagaa 60
gcaagtatga ctttctctcc tgtggcttta cacaacctcc ttgaaattcc aagagcaacc 120
ctcccagcta aagtcttctc agatgtgaca cgatctgcac aagcagaggc ggcacagggt 180
ttggcttcca gttgggaaat gaagctccaa gggcagccct actatggcgg gctgtgtgac 240
ctgggccaag ccccttgaca tctccagact cggcttccac atctgccacc accaggacac 300
tggattgaat gttgggtacg ttgtaaggca agggagacac agaagtccta aaggcaataa 360
agcttttccc cactgcccct cc 382

<210> 380
<211> 364
<212> DNA
<213> Homo sapiens

<400> 380
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tagctgggac tacaagcatg taccaccatg cccagttttc tgcagcagtt tttataaacc 120
aaatttttcca aattagaaag actgaccaaa gaagcacttt tatacgagga ataacttacg 180
tatggagaat ctcaacttgg accagtcaag accaactcca gcgatgaagc cagaatgtaa 240
tatatctcaa aaggctaaag aagtccattt tcccagatgt aaattataat taaaaaatag 300
tgagccaaac tctaatatcc caatgtgata atctttcaaa taaaaatatg ggctgtagtt 360
cagg 364

<210> 381
<211> 318
<212> DNA
<213> Homo sapiens

<400> 381
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aaggagtccc aaagctcgcc atgactcaac aggaagctct ttgtgtcttc ctttctacac 120
catgtctgac aaagaagctg tcttaagttc atgggcctct gtctcttgcg tgaattctga 180
agtcagtgaa gcaacaatga tgtcattgct tctgaagacc actgttggct gagataatga 240
agatctcttc acccaaaaca ttgccatttc tgcagcatac atttcctacc ctttcaaata 300
caaaagtatt ctaccgat 318

<210> 382
<211> 463
<212> DNA
<213> Homo sapiens

<400> 382
ccagcagaca tcaaggactt ctgaggagcc tggtaccttg cataggcact atggaccctg 60
ttttgcttaa cccacccaac agccaatttt agcagacatc ctagttttgc aggtgagaag 120
agctgaggta cgaagaagtt ttgttaattt ttccagttca cgtaacaagt aaatgggaaa 180
ccaggatgaa aatcaaggtt tatctgtcgt cagactgtta ctcataatca ccattcggag 240
agttcanatg tgggacaaga ttctaactcc nnccttctcc caaatggtta atntgccagg 300
tgccctanag ctacatattg tcttatttgt gtgatnnact gannctgnct gaatnttana 360
agccttgtat cttntgnant nncaaanaca naagagnccg nggggnntat ttaaattnga 420
antnaaccgg cctgannngc cnaaaanggn ggggcttccc agg 463

<210> 383
<211> 220
<212> DNA
<213> Homo sapiens

<400> 383
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ccaacatgcc agccatgtga acaagcccag gtggcaaatc acccagcctc agtcaagctt 120
tcagatgacc acagccccag ttgatatctg actgtaacca catgaaacac caaactctgg 180
actcacagaa atcatgagat aataaacaat gattgtttttg 220

<210> 384
<211> 434
<212> DNA
<213> Homo sapiens

<400> 384
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cttagaagct caatcctcag gagacagtgc actgggggtt gccaagggga cctgaaatac 120
cggtttgcca caatcctgac caaatcggct cccagggctg agaagggaga aggtgtcagt 180
ccattcaaaa cccatcgtgg ctgattttga agtggaaaaa gaaaaaaaga agcaagaaa 240
agcattgctc agcaatgggc aggaagaaga gttaagaggc tgagctcttc ggcaagaaat 300
gccatagctc tttcaacttg gacagagcca ggaccacagg ctggttgtgt caaaaactgg 360
gtgttcttgc ttagtgcata aggtttggtg gttttcctcc ctctttcctt gagccctggc 420
acttggggac cctg 434

<210> 385
<211> 268
<212> DNA
<213> Homo sapiens

<400> 385
attgtgaatg ccagcagaac agctgacccc aaacagcttg aagaccccca caacagaact 60
gaatcagcat gaaaatgcag tttctccacc tctctgttcc atgacttcac cctgcactct 120
tccaccaatc aatggtctcc acactttggt cgacaccaaa acgcttaaga acccaaccct 180
agccccaaat tccttgggga gacagatttg aggagtcctc ttacctcttc atttggcagc 240
cttaaaatta aaactctttc tttgcttc 268

<210> 386
<211> 542
<212> DNA
<213> Homo sapiens

<400> 386
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ctgaactcca aacgtactga gttacctgca gttcctgtaa tccagcatga ctttgtcctc 120
caagcctttg ctgtccccac tcatccttca gttcctagct caggaatcat ctccatcaag 180
gtttccctga cttctcccat ttcccaagtg aggcgttcag agagtcctgt gcttaccttt 240
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tgagcaccct gagggcaggg actgcagctg ttatctgggt acatacaaca ccaaataaca 360
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ttccttcccc agcatgcctt ctctgactat ccccacctcc ttccagaagt actcacctaa 480
tccatgcgga caccatagac caagtgcatt tataaaactg gtttatataa ttaaatgggt 540
ag 542

<210> 387
<211> 282
<212> DNA
<213> Homo sapiens

<400> 387
gtatantant tcttatangn nngnnnnnnn nnnnnnnnnn gggatgctcc ttcctggacc 60
cagccaccca ctgggaaaag cctaagccac gtggagcanc tacatagaag agggccgggg 120
ccacagctac agccagcagc tcctgccagc cacgtgagag agctaccttg atgttccagc 180
ctccagagat ctaagagctt ccagacatct accaccccag ccacaccacc tgagccaatg 240
tcccacagag tcatgggaga taataaaagg ctgttgttct ct 282

<210> 388
<211> 263

<212> DNA
<213> Homo sapiens

<400> 388
aggcaagttc tccgttgccc aagctggcct ccaactcctg gctcaagtga tcctcccacc 60
tcggcttccc caagagatgg ggttacaggc atgagccact gtgcctggcc tcacaagatg 120
ttgttatctt tgttttacac tatcaatgcc catgcgtcct tacttaatta ttaaccactg 180
tattgctgtt cattcttcct gcatctcata tcttccatca gggatcattt ttcttctaca 240
taaaataaat catttgtaat ttc 263

<210> 389
<211> 292
<212> DNA
<213> Homo sapiens

<400> 389
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gggcctggac catagaactc acacataatc cttcatgttc ttatgtgacc acacagatga 120
acaaagcaag ccaagtgtgg aaacgtgtta aagatgacgg aaccacaaga tggaacaagc 180
ctggatccct gaatccctcc ttggaggatt agtgcccaca aattgtaaac agccacccag 240
atctcagcga gcaagaaata aattatacct gaatgtttta aaaaaaaaag gc 292

<210> 390
<211> 244
<212> DNA
<213> Homo sapiens

<400> 390
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agtacataca gaagaacagc atcacaccac atcctatcac caaggccagg attctgtgcc 120
tccgcccccc tccccacctc cttgaaacgg gggaagtagg gggaagagtc aattcttctt 180
ggagcacatg agatggtagc ttgctgtgtt gtcctgaaag aaaacaaagt ttgtaaatca 240
ctgt 244

<210> 391
<211> 436
<212> DNA
<213> Homo sapiens

<400> 391
ctgaggaata tatgattggt ttcttggaac aatttcacag ctggcatgga actgaaaccc 60
tgctactcag gggaaattag gatcagctct tgtccagttc aagctgactc cactgagcct 120
ccaatggcct gtatgaatgc ccaatgagtg ccctttttgac atcagaaggc caaaaactcc 180
accctcagat tgtgccaacg acaccatctt gcgaacgtgg atcctatgaa aagccatgaa 240
gcttaactgc actcgcacag atcagcaatt acctcacttt tccttaccac caattaactt 300
tttccatgca ttggctgcct tgcttcttta ttccacaaaa atccttatgg ccccactttc 360
aaggagggag aaatttgagg ggngttatcc cacctcctca cttggctgcc tcatgaataa 420
aatcttttct ccctgc 436

<210> 392
<211> 178
<212> DNA
<213> Homo sapiens

<400> 392
aggctgttgt gatatcctgc atggacaagg aaatgatgtt catctaatac acccacttgg 60
gaacactttg atgcattggc tatgattgtc tttctgtttt ccctaccctc atctctagcc 120
ctgtcccagt atgagaacat ggaaactcat tttggaaaat gtgaaatgag tgatcccc 178

<210> 393
<211> 263
<212> DNA

<213> Homo sapiens

<400> 393
attgatcgca gagttgaaca acagagaatg tgtgcacagt gccaggcaca ggtgtggtca 60
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gctgcatggc aggtgaccat tatcaccagt gtcgccagcc aggtcacctc tctgaatttt 180
gtggttgcaa cctccatgat tccctagagc tgtttttacc cagaactaat gaaaaattct 240
gcacattaaa ttcatgctat tag 263

<210> 394
<211> 267
<212> DNA
<213> Homo sapiens

<400> 394
ggcccctaac agtgtcatag gcctgatgga gcagcggaac ctgcctgagg gtaaagctga 60
agttcctcag aaaccagacg gccttacagc ctcttcactg ctctttgaga tggaagagaa 120
gaaatgcaga tgagtgcttt ctgctacaaa tctcatctct ccaagctgaa gttgccaagg 180
aacatgccat cactgtaact gctaaaaaca caacgtataa tgaaatgcat cttctacaaa 240
tgaatctgtg aatacagaat agcctac 267

<210> 395
<211> 180
<212> DNA
<213> Homo sapiens

<400> 395
gcacacatag ttccttttgg cgtcttatct tctgaagctg cctcaaggcc aagcaaagaa 60
agttgttaaa aagttaagtt acttttcaca gcctgcaaac ccttcaaagg caagaactca 120
aatagaaact tggaaaggca gataagccag aaaagtgtac taataaacgc acttaatatg 180

<210> 396
<211> 428
<212> DNA
<213> Homo sapiens

<400> 396
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tatgtcataa aagattagat caacctgtaa ccagagccta ttaagtgatc tccagcaact 120
gtctccgagt tggaagtgct agccaaagaa tttcagtgat tgcgttttgt gtacttacac 180
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ggccaagtca ctgcagaagt ttcttgaaag ctcaaatgtt gccttttcct aaactaccca 300
tggccccacc ccacctcatc ctgtgcctat aaagacccca gactcaatca gcagagagga 360
gaagcagctg aatgttggag agaagggact tgacttcaga gggacagctt gatggagtaa 420
ccggagaa 428

<210> 397
<211> 285
<212> DNA
<213> Homo sapiens

<400> 397
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atgagtctca tccttgcagc taatcaaatg tacnanagca tcaacagaat taagatggtt 120
ancgaggtga ggccttgaaa tcaacatctc cgcctccttg cataaaccct tcattgagac 180
tcctcttcca tttgggcaac ttgatgtggt tcaagagcat ggagaattga tctcttaaga 240
ctcataaaat atttgcttct tcaaaaagaa taaaggaact gaaac 285

<210> 398
<211> 169
<212> DNA
<213> Homo sapiens

<400> 398
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gaaactaaga gaacaggcca cagagtgtct tgcaatctat gctgctagca agtgtctttc 120
tcatgcctga tgttatacaa aaactagcaa taaaggctta ttctttcct 169

<210> 399
<211> 224
<212> DNA
<213> Homo sapiens

<400> 399
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ctaagagatg gccactcagc ttctggcatt atcactctgc atctactttg ccaagcttct 120
tcttttgaaa cgtcttgtgt aggcagtagt taagaatatg ccacccagaa gaataccaga 180
tgaataaact tacaaatatt ttgaataaag ctcaatctaa caat 224

<210> 400
<211> 466
<212> DNA
<213> Homo sapiens

<400> 400
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aagcaaaatt acctgaanaa aggtncgaaa aactggtccc aggnccntaa aatgctgngc 120
tnnnaaaang nnatntnggn nnaaaaaacc ngnnancccc ttcntccccc ntccagaaac 180
ctanaattna cgttctacna cttccacaac ccaattccaa cttcctttnt taatatgtgt 240
aangngtatc tgccccatgg gccttctgga tgtgttcatc aattctgaaa aactctgaac 300
tcggaagctc agtgagcccc agggtttggg gtaagatatt acggacctgc nctttnagcca 360
aaagtgcttn cgctcactct actactgnnc tactgnncct gacggnngat gtcccncaaa 420
gccnccttgc tgtggggcag gggggccccc tgtccttttt ggggaa 466

<210> 401
<211> 350
<212> DNA
<213> Homo sapiens

<400> 401
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ggagagcggc gcctgaaccc tttcctacca tcaagaactc aagaactcag cctaataaat 120
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gggatgcaaa cgatccagtg gaggcctccg aggccctaag gatgaagcag ctggagacag 240
aagggcctgg gtccctgaat ggctgggagg aatagagccc cagtgcagtc tacttgcacc 300
cccaccttga ctctgacata ggcagaaata aatttttaca ctctaaaatc 350

<210> 402
<211> 133
<212> DNA
<213> Homo sapiens

<400> 402
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aagcttgtgc tcacaatccc tgccattaca attctttata gtatgtaagt actttaataa 120
acattatgaa gcg 133

<210> 403
<211> 330
<212> DNA
<213> Homo sapiens

<400> 403
gaaggaggat atccctgcga tcaccaagcc tctaccctta tcttccaaac cagtcactta 60
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tcaatacaag atgctttact ttgtcacaag aagcatataa taaactcaaa gctgcaagga 180
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actttttgtg ctcagatatt atggttgtaa atgaggattt ttttcctcac ataagaatgt 300
atctagtcca ttataaaatg ttattgatgc 330

<210> 404
<211> 242
<212> DNA
<213> Homo sapiens

<400> 404
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ggaagagcca gctagtgaca accggacttc agggaagatt acctgcccaa cctgacccct 180
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cc 242

<210> 405
<211> 289
<212> DNA
<213> Homo sapiens

<400> 405
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gtcggcctgg gacacaggca ttctggggct caccaccagg tgttccacgt gtcaccacta 120
gacctcccaa ccagggagcc ctgccgctgc cccagcctgg agacgtgaca cttctcccag 180
ccaggaggct ccagtgaaac cagggattcc ccaggctcac cctgactcct catcttgtta 240
acgtatttaa tcctcatcct gtacatgaaa taaatatttc atctcatct 289

<210> 406
<211> 436
<212> DNA
<213> Homo sapiens

<400> 406
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cagagggcca gtccccaggt gatgccggta cgctggagaa ggcctgggaa gatgtgcgga 120
gacagacacc tgggacacct aaggaccaag cccagagcca cgctgctgct ttcccagctg 180
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ttcaaaaggg tgctgaaaaa cacccttcat ccccgatggc ttagcttgtg gaattcacgg 360
gtacttgcat ctgaccctca tgagtctatg tagaaaaacc tggttgagga actgtttgtt 420
gacacccaca tcagct 436

<210> 407
<211> 179
<212> DNA
<213> Homo sapiens

<400> 407
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aggcactatc atggaagtcg aaactgggtc ttcaccacat accaaacctg ctggtgcctt 120
ccttgatctt ggacttctca gcctccanac cngtaaggaa ataaattctt tttttaaat 179

<210> 408
<211> 419
<212> DNA
<213> Homo sapiens

<400> 408
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agaatggcag ttatgaaagc cttgaataag ataaaggaag aggatttcct taagcagttt 180
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ggtgctgttt ttgtagctgg gagatataat aaatactcca ggaatctacc acaaactcct 300
tggataattg atggagaaag gaagctggaa tcttcagtgg aagaattaat ttcagatcat 360
ctgttggcag tatttaaagc agagagtttt aatttttcat cctctggaaa aaaaaaaag 419

<210> 409
<211> 409
<212> DNA
<213> Homo sapiens

<400> 409
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ctgtgcccaa cctgcgaaaa ctgggaagaa atgaagaagt catcctcttc ctgagacaga 120
gcccagcagc cttggggcgg ctgagagaag atgggatcca cgtggcccat agcgcacccc 180
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<210> 410
<211> 443
<212> DNA
<213> Homo sapiens

<400> 410
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gttacgcatt gcctgtcact aggtatgagg ctgcctccga tttccacact nagaatcang 120
gctgcagngc cctttgtgcc catggctgnt gatgcacaca ggattcttnc aaaacaagag 180
gccctactct gtgactgtna gccttgccat caacactnct ntttggagna nagctncctg 240
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aaagtctgag gcctggtttn aanccaaacc cnggcaaggc ttttgagaac tccaccnttg 420
ctgccatctt acgtccaggg agg 443

<210> 411
<211> 96
<212> DNA
<213> Homo sapiens

<400> 411
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tgatcccatt acaaatacat gtgatgacat ctgttg 96

<210> 412
<211> 306
<212> DNA
<213> Homo sapiens

<400> 412
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caggtggtgt cactgtggct ccatcacatc agctagacct ggccatgcag tcccaacttg 180
ttacctacag ttccagctgc caactcaggc catctcactg aatgaaatac ttgcttcaac 240
attgaagatg tttcctctgg ccactcagag gaaacaccct ataatgaaca ataaacaaaa 300
ggactc 306

<210> 413
<211> 219
<212> DNA
<213> Homo sapiens

<400> 413
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gagccaggtt ccacaatgct tgatgantac aatnttttca ngaanacagc anaacagcat 120
gaagaaaaga aacctggatc tgcaagtgcc taagcagtga gcaagacccc accaacactn 180
ggccactnct tcttggacca tccttaataa agttatttc 219

<210> 414
<211> 457
<212> DNA
<213> Homo sapiens

<400> 414
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atcaggagtc tcttaatagt ctcccaccca gttacaacat attgctgtaa tcccacacaa 180
cagctgaaac atcttttctt catttctttt aattcctgta gcatttgatg tctccaccgt 240
gtaatttaca tttaattgta agttgttttg catcatttaa tagttgtttc aagtatgaat 300
gtcttgcctt cccaagaaag attaaaataa gaatccttta aaaacaagag cttactggng 360
ccagggccng acttagactt agagtaaacc ncaactactg gcttcacttc aagctgacct 420
aaccatcttc ccagcgaaga cggncaacct ggaacta 457

<210> 415
<211> 356
<212> DNA
<213> Homo sapiens

<400> 415
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tttgaacagc gccacgcttt cctatatatt tttatagcag agcctaaggc acagcctggc 240
acaagtgcgg gaaacaagtg tctctncatg ccagctccaa gcggaggctc aacttttcat 300
tgntggttgn caaaaggggc aaanagcccc tgggaaaaac caaattttga caggga 356

<210> 416
<211> 99
<212> DNA
<213> Homo sapiens

<400> 416
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ttttaatcgc cgctcattaa aagaaacact gactgggtc 99

<210> 417
<211> 173
<212> DNA
<213> Homo sapiens

<400> 417
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caccacttat gacacagaag actctaccaa aggaaatcaa actacagaac agcaacaaaa 120
ctcaaaannn gnncatttgg cttttgtgtt attaaaatat tttctcagca gac 173

<210> 418
<211> 463
<212> DNA
<213> Homo sapiens

<400> 418
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aggacagaaa ggaagcccaa acgctttaca tattgcctgc tttacacccc aggctcaagt 120
ccagaaagtc cctgtgatac aactctccag tgatttcccc tgaggtccaa cctagtaggt 180

gcttaaaaag tctttgttgt aaattaataa attaatccaa aaccaccaca ctgctatttc 240
ctcctaccta tcttcctgtg cctatcataa gctgtatcac ctggggaaaa aacatttttc 300
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aggaaataat cagatttaga taaagatagg ngtatgataa tattcaggca atggggtttt 420
caatagtgga aaggtgggat caacctaatt tgaaaaatag cca 463

<210> 419
<211> 474
<212> DNA
<213> Homo sapiens

<400> 419
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gagaggtctg ctgggagact tcctgaaact gctcttcctg gaaggaggga aacaaacaaa 180
acaacaacaa aagaacttta caagagaaag ctttttatcc cagccccttc ctactcccat 240
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tgncttntnc aganctnttg gcnnggggna aaaaatnaaa nggcntcntt gnttaanccc 420
ctggganact anattntgtt ctttgccact gaatgcatcc taatgctgga actg 474

<210> 420
<211> 477
<212> DNA
<213> Homo sapiens

<400> 420
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ngagagcccg atttgttngc tttgngcccc tggantggaa tcccagnggg aagatngnna 120
tgagagtcna ggnctacgga tgttnctata aatcagacgt tgctgncttt gatggccnna 180
nctnacttct gnacaggntc aatnaaaagn tgatnantac tntcaaanat gtgatctncc 240
tgaagttcaa natcatgcna ggagatgggg tcctgttcca tggagaaggn gggggggag 300
accacatcac cttggaactc cagaaaggga aggctcgncc tacacctcaa tttggngngnt 360
tgtagttctc cttgaagagg tccttcacat ccctttgtaag ttggaaaaac attccatgct 420
catgggtagg aagaatcaat atccgtgaaa atggccatac tgcccaaggt aatcttg 477

<210> 421
<211> 292
<212> DNA
<213> Homo sapiens

<400> 421
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cctctggatt aaaagggatg tttggatgaa gcttcaatct caagaagagg caagagaaaa 120
ctaaagaaaa agattattct acagaaacaa cacatcactg gatgcctctc accatgcaat 180
cctctgtgca cttgagaaga agacaagact ctcctatttt tagatgggaa agctgaggca 240
aaacggatgc acttgggcaa aatcatttga taaaaatgga agctgaacct cc 292

<210> 422
<211> 98
<212> DNA
<213> Homo sapiens

<400> 422
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gacatgtcat gaattcctga accacaataa atctgtga 98

<210> 423
<211> 103
<212> DNA
<213> Homo sapiens

<400> 423
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nttctgccta agaataagaa gaacttaata caaatggaaa att 103

<210> 424
<211> 376
<212> DNA
<213> Homo sapiens

<400> 424
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gagtggattt ccacgtattg ttctagatga tggagaggcc tgaagagtga ggagtgggga 180
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tcttatgtgc caagtacttt atgtatgcat tatcataaat aaagcttttc accattncct 360
taattctttt attttt 376

<210> 425
<211> 78
<212> DNA
<213> Homo sapiens

<400> 425
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tttaggagtg aataaacg 78

<210> 426
<211> 330
<212> DNA
<213> Homo sapiens

<400> 426
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gtgcagatac tccataggtg cttaggagtg tnagtgttna gngactgctg caagaaaaga 120
ggagatacga tctgatcact tagacttcaa atccaaacct tgaaaagtcc cacccagtgg 180
aggactcttg ccgccttgag agaacacagc tgatgtccgg aagcaatatt gntaacntta 240
ccaataantc caatcaaacc ccaaaaaaaa aaggcccggn ggcccattta ncttggantt 300
accaggctga acttgnttaa aagggggga 330

<210> 427
<211> 291
<212> DNA
<213> Homo sapiens

<400> 427
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cttccaacct gctggcagtg acggatggca gtgcagaggc acacaatggc aagtgcaggc 120
gcgtcaccag ccttgcagct ggccttccaa agaaagaacc aaagtcgaag tctgtcctga 180
cagaggctga tttaattaag gttatagcaa agggcagaac tgcctgtggg ctgcattctc 240
tgcagagggc caaagacaat gcattaaaat acttctcagg aagaaaaaac c 291

<210> 428
<211> 304
<212> DNA
<213> Homo sapiens

<400> 428
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tcagcaatgg gggaggaaaa cgagcgcact acggggtaaa ggaggtcacc caagatctca 120
agttcacgag tggcagcctg gattcaagtc cctgcctgcc tccagaacct gagctctgaa 180
acgctggact aatcagaacc tcttggccct gaaaaatgag gcctattgaa cagagacatt 240

tgtaagaaaa gggactatta caacctattg taaagtaaca agcaaataaa aaatgaaatg 300
gccc 304

<210> 429
<211> 248
<212> DNA
<213> Homo sapiens

<400> 429
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gggctttcct ctctcctgat gagatgatgc aaatggactc catagagaaa cgctgcccgt 120
gtaacaatgc agttacgcaa cccggtgcat gacacatgaa ttgcagcgca cctgagatcc 180
tgatgaaatc ctgggagcct ggagctgtca aacatggttt taaaaaataa agggaataca 240
cccagccc 248

<210> 430
<211> 460
<212> DNA
<213> Homo sapiens

<400> 430
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accaaaaaat tcattattgt tggaaaagct tggattattg gattttgggg gaccttgtgg 240
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tccctttgg cctttcttgc catggatttg gaaaaagttt tcccttggag ggcccctccc 360
aagaaaagcc caaagaaaag aatggcccgg tccattgcct ttccttggta acaagtcctt 420
tcaaaaaaaa cgaaatggtg gtccaaattt aaaaatcttc 460

<210> 431
<211> 176
<212> DNA
<213> Homo sapiens

<400> 431
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ttctcaccac tgaggctaca aaagatatct acacctgcaa ccctttccct ttttttcttc 120
ttccctttg ttatgatgta taaagtgtcc cttatctgat aaagagctaa tcattc 176

<210> 432
<211> 301
<212> DNA
<213> Homo sapiens

<400> 432
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cagagcaatg catttgtgtg atttgcccaa ttgtgcatga gtacagtcag catggaaatc 120
cagttcaaac tgcagaagat cagcacctgt gagctgaaat gtgcatgtgt attttacagg 180
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gagattggat tactgcagct gataaacatg gaaatgagta attaaaacat ggtgtgtaag 300
g 301

<210> 433
<211> 443
<212> DNA
<213> Homo sapiens

<400> 433
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cctccactgg ggaacaagaa gtgcgttagg ctgatgtact ccactccacc tccatacgtg 240
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tacccactct ttgagtcttg gncccagggg ctgntgctct ctntntctca aatgatttct 360
gtgttctcat ttgtctctgc cttctctggg aatctttggt gccacagggt aatctcctgt 420
gtgtcactcc tgacttcgga agc 443

<210> 434
<211> 288
<212> DNA
<213> Homo sapiens

<400> 434
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tagagaggag agactgctga cctgctaact gaaaatataa gcaagccctg acatgccaca 120
ggccgtcgga agagacattt gcttttgagt acccagccta ttctactctc tgacttatgt 180
agatgggaca aatggtgccc tgggcacact catctacaca tcagcctgaa ttagctagta 240
aatcacaact gcagtagcta ataacagcca taaagccttt tgaatgtt 288

<210> 435
<211> 383
<212> DNA
<213> Homo sapiens

<400> 435
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tgctatgaag ttaaaagagg aat 383

<210> 436
<211> 251
<212> DNA
<213> Homo sapiens

<400> 436
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atggtgaatc acaatttttt catctgactt ctgttctttg ggctctgact cttcatcaga 120
atcaatgtca agggccttct ccttgtagtt ttgatacagg acagcatttt ctgcaagaaa 180
acaaggccta tgtgtcacta attgttctca atcattatgt tacttgttct aaataaacat 240
catatgtacc c 251

<210> 437
<211> 220
<212> DNA
<213> Homo sapiens

<400> 437
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ggatctgaag ttgctggaga agattttgcc taggctggcc agcaactggc agacaagagt 120
catcctttca caatgctgga gacagtagac cttcttcagg accacaagca agtcaccatc 180
tctgggtcac agcttcctca attaaaaagt tagaagatag 220

<210> 438
<211> 229
<212> DNA
<213> Homo sapiens

<400> 438
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acaaatattg attttcaaga tcaggaaaaa taccgggacc agaagacaaa tttcagagcc 120
acctaaattg tggagtctaa taaaagattc ctttctccta atgatgtgac catccaaagg 180
atacactctc agtgtaaacg taaacccaga ataaaatttt atcatcacc 229

<210> 439
<211> 309
<212> DNA
<213> Homo sapiens

<400> 439
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accaatgctt cttcagcttg aagactaaca tctagaagag tcatgaagtc taaagtcaag 120
aggagtctta tcttctagaa agtttttcaa acatcccaac ctcaaaaagt ttggctaaat 180
ggtgttcttc tacagcccca cacatgcaaa catctttatt gcacttgtgt cattattttt 240
tcttcgtata tgtgnttttc tataagtaca tttatatgaa ggnatatttt gaaataaaga 300
cacttcctc 309

<210> 440
<211> 756
<212> DNA
<213> Homo sapiens

<400> 440
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tggggggaaa ncaaacgggt ttnaaataaa ctnttnatat anaccccccn cncctttggg 120
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<210> 441
<211> 599
<212> DNA
<213> Homo sapiens

<400> 441
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ggcaaggngg ntcacacctg taatnccacc ttttggagnt gacccggcag ataacctga 599

<210> 442
<211> 512
<212> DNA
<213> Homo sapiens

<400> 442
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cctggcctat atggttgatc cttctagtct cgtggcagaa ctttgtagac accaagcgag 180
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ctcttcaata aagtaaaaat gggtcatgct gg 512

<210> 443
<211> 223
<212> DNA
<213> Homo sapiens

<400> 443
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agtcaccttg caaatggatc ctccagccca tcaggtctac aaataactga agcctcaagc 180
tgacaacctg actgtaatct cataaagtca taattgacca act 223

<210> 444
<211> 618
<212> DNA
<213> Homo sapiens

<400> 444
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ccgcctccca agtagctgga actacagatt ttaacaatca gactcaggtc aacagtggtt 120
gagataatgg cccataattg gctccagaat gcaaacgtgg catttctcca ggattccatt 180
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accgcttgac ccagaagg 618

<210> 445
<211> 459
<212> DNA
<213> Homo sapiens

<400> 445
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tgttgagaac atagcaaaag cagctcttct tgacaaaaat ggaaagaaac atcctcaagt 120
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tggaggaaaa ccaacacaca gtaccattta attcttttta aaaagatgga aaattatacc 360
atacccngaa ttactaaatt cttaaaagag gggtttntn gcattccatt tgnaaaanaa 420
ngtttcccca tgttctttta aaaattcatt ttaaaccac 459

<210> 446
<211> 403
<212> DNA
<213> Homo sapiens

<400> 446
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acaccactgg ttttcctggg tctccagctt gtagatgact aatcatgaga cttcacagcc 120
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tggagtacca taccaaccct ggactatcta cctccagact tttacatgag taagaaacac 300
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gaaatacctg cattctcttg aagtaaattg ctttcaaaaa cct 403

<210> 447
<211> 635
<212> DNA
<213> Homo sapiens

<400> 447
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tattcctcac aaaagccata tgtaaaactg gctgctccac aagggctggg atcctgtgtg 180
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cgaataaatg aatgaaaacg tgctcagcac agggaggtaa aggcaccagg accccatgga 300
gagagagtac atgctgagtt ggctacatct gtgccaaact gtgaaagatg acaatggaga 360
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tgctcttctt gcctgacaat tcgaacaagc agcttgactc tgtatttgag gccccactcc 600
cttttggcta actagaccan actaatttac tcatt 635

<210> 448
<211> 81
<212> DNA
<213> Homo sapiens

<400> 448
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gccccctgca caaaaaaaga a 81

<210> 449
<211> 616
<212> DNA
<213> Homo sapiens

<400> 449
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tttaccgtcg ccactgaatt tggccaccct ccccccctcta ctgtgcttct gcgctacaac 180
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gctgcttnct cccacaactt ttgtttggct acaagatgat atcataccaa atcctcagtg 480
gcaaaatgtg tttctnctga attcataaca taaaaaaanc cattaaaagg ggggtangca 540
tacctgataa ctattactgg aataaaaacc cggactcacg ccttagaaan aaaaaaggtt 600
atcaaagggc aacaaa 616

<210> 450
<211> 617
<212> DNA
<213> Homo sapiens

<400> 450
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aatgngccca gtgataatga gtagnaccta tgngggactc ttnancttaa angantggca 480
cgaaagatta nctttnttat tgctctngac aaaaaaantn gnttttnttt tggngggaat 540
ttgggnatct tcttgggact tnttttttc cgatggcttc aaatcctggt ngacccttnt 600
tgnngcatgg ctcaatt 617

<210> 451
<211> 203
<212> DNA
<213> Homo sapiens

<400> 451
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tgaaacctcc ccttttcctt acttctccct ctgttcagaa tgtgtagact tctctaagct 180
ttgttaaacc tgtttacaac ttc 203

<210> 452
<211> 445
<212> DNA
<213> Homo sapiens

<400> 452
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gatgcagctg gcttcactga acataatttg ctattagcat cttcaggaac acacactgct 180
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cctcactcca gaatgccccc aggtacctga ggatgctcca gatttggggg ctgcaccgtc 360
tgtggtttct ctacattaaa cagtattttt gtggagtcag ggtgaggga gtatgggtta 420
cttttaaata taggtttgcc aactc 445

<210> 453
<211> 460
<212> DNA
<213> Homo sapiens

<400> 453
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tgtctgggaa ataaaaggtc agagagttga ttagcaccat caagccccaa tacccagaat 180
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tgggggattc cctcgcccca ttttttatcc cattgcccct tctgtgccag tctcttcctc 300
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agttttctgc aggcaacatc tgtgtgcatc ttagttgtca caggtctggt caaatgtaga 420
gatgaataaa ttttaaaaat aaacaactac aaaaatacac 460

<210> 454
<211> 261
<212> DNA
<213> Homo sapiens

<400> 454
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agtggcagca agatgatgcc agccgcagtt accatctgat tacaacttca taagaaaccc 180
tgagcaaggg ctgcccagct gagttcaagc aacgccccag acctgtgggt gatgataata 240
aaattattgt tgttttgagt c 261

<210> 455
<211> 591
<212> DNA
<213> Homo sapiens

<400> 455
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ttccactaca gctgagtcag aaaggtcgct gccccgtggt ggcactagac gcagtggacc 180
tggcaagcaa atgtttccgc tattagctct cagcaacaga gactcattta tggtcacctt 240
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ctgttagcag agtggaggag aaaatacaca gcacaaacaa cgtgaaaaaa tagttactct 420
attcattaaa agctgtaact tccagattgg acttgagaag cattaaagca acagaggacc 480
ctcatctact atctgtattc aagcatgctc atgaaaaaca cgctgctcaa ctggacttan 540
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<210> 456
<211> 475
<212> DNA
<213> Homo sapiens

<400> 456
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caaaacccac gctcttttca ctgtgatgca cggctaatac tgagctgagt gatgggaagg 180
gagctctctt tgngggattt tcangatacc ttcaaagatc angntggntc tgtttgcaga 240
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gccctttttgc aatnggaagt tatttaacct gatcacanca aaatgaaaga ttatttgaaa 360
accngggatg tgaaattctt ggaacccaaa gaaaattatc ccatgnttct ccaagnacct 420
ttgccacccc ttgtggncct gctaggncac atggacccca aacctttcca gaaga 475

<210> 457
<211> 145
<212> DNA
<213> Homo sapiens

<400> 457
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tgatgatgct ngtggctatg agaca 145

<210> 458
<211> 434
<212> DNA
<213> Homo sapiens

<400> 458
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tcactccctc tgtctcatcg aggagaatgc tccacccagg agcacagaat gaaaggcaca 120
gagtatagtt tccagaatcc ccgcatttca gtgttcccaa agggctgaat tcttgtcaat 180
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ttgcattggg tcagtgagaa gttttatctg ttacggcagt tacttctact ttaataaata 420
caatgcatta tctt 434

<210> 459
<211> 493
<212> DNA
<213> Homo sapiens

<400> 459
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cacttatcaa gcagaagaat cacagaagaa tacaataaat ggtctagaaa ctgcagtgat 180
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gtggctgaac atggagacca gcagaacagt gccggcggaa tgacatggcc gagaaagaga 420
gaaagangag ggacattttg gaccccaagg gaaatttggn ccggggtggg tngaaaaaaa 480
atttggccct tga 493

<210> 460
<211> 404
<212> DNA
<213> Homo sapiens

<400> 460
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cagaagacag ctactgagat tctgcagatt ttctaaaagt gacatttcta ttacacattt 180
cttcttttca gcactgtcat atgtaatggt atgcattatt gcgttgtgta cattttgtga 240
tacatcatca atctgctaca ctacccccatt aatccattca ttcaataaaa tacattgtta 300
tgtgccagat actcttagac aagtcactta cccenttagc ttcatttcct taccccaaaac 360
ttgnggatca ttatacatgg ttgataacta aggaaaggat tttg 404

<210> 461
<211> 583
<212> DNA
<213> Homo sapiens

<400> 461
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gggtggatgc cttgcctttg gatgggaaga atccttgcaa gtcaagacta cattccttgg 180
caccaaggtg gccaaagccc gtaccgaact tggcttggaa gcttaccttg ggcaccaaga 240
aagaaatgga cctttcttct tattgaacaa tttcttcaaa cttgggccaa ngggttcact 300
ttcaaacttt tcttaaaanc ttggnttncc aagcccacac caagtcaagg gggaagtctt 360
ccttggtatt ggaaangnac ttggggtngg ttttgcttgg aaaccgggct tggaaattgg 420
aanggggccg gggaaaccgc caccccacn ttacccaacc ggtnggggng gaaaattggg 480
gcattttacn aaccgnaaac aaagtccccc ttggcattgg aaatttccct tnttttttgg 540
ggggaaanaa agtnccccgg aacnttgggc aagaaaccgg aac 583

<210> 462
<211> 339
<212> DNA
<213> Homo sapiens

<400> 462
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gcacatgttg cctgtctccc ggtgacagaa gataacagag gactaagagc gcacatatac 120
ctcaagagcc ctaaggctgc cacaggaggg taaacaactc cacccagcac tgctccaggc 180
cggcacaacc atcaactttt catgagcggg cccactggct gctgtctgga atgaagaatc 240
ctatgttgct ttccagcctc acatttcccc tttgtgtact acaaaatagg agctgtttca 300
ttagaaacat aaaacaatga ggaagaagct gttattgac 339

<210> 463
<211> 662
<212> DNA
<213> Homo sapiens

<400> 463
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aanatgcttc aanggaggga gccaaggaaa gtggctnttg cttggggggc gccccacaac 120
ccttgctccc ccgatgtcca cccgtggatc cacatcccgc cagccgaaga cctcccgtgc 180
cttggaccat tgtcgtcttg ggtcccttgt tcaaacaccc ttctttatgg aaacaccttg 240
cttgccttgg ggctttcata agccatttcc gccctacttc ccgtggaaaa gttctaaggg 300
gacaagggga aagaaatggg gtttgggcgg aaacgttgga acccgggggg ccccaaaggc 360

ccttaattgc ccttnccacc cggcccaaan gtnggccctt ggaaacattt cttnggggcc 420
cccttngaat tttttnggggg gcattncttt tcattggaaa caatttttctt ggntttnatt 480
tcaatcaatt tcccaaaatn ggtttgggtt cggttcccaa nggcccccaa nccggaattt 540
gnaattaaan gggannnggc ctttcntttt ntaangggcc caanggaaag cntntttggc 600
ccccggnngg aaccttgttt tttncccacc gtaaccnttt tatttttttt ccatttttcc 660
tt 662

<210> 464
<211> 459
<212> DNA
<213> Homo sapiens

<400> 464
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agtttaagat ctaagagcaa tactcaaaca gaaatcaaat aaatgtctat gacaattaag 120
gcaaacatac tcatttgtct acaagcaaag agcatttttgg aaagaacact cccttgttca 180
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gttgacttct gattaacccc agtctgggga atgcctctaa gatttctatt tttatttatg 300
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cttaggctat gacacacata acattctttc ctttttctgg anaggggggc ttcaattggc 420
cttatacatt ccttntaaag cacatatacc ctttctctg 459

<210> 465
<211> 476
<212> DNA
<213> Homo sapiens

<400> 465
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aatgacagtt atctttacct atcacttcaa gttatttctg tcaagaggta atgacagtta 120
ctgaaaaaag aagttctgga ccttttttcat ttgcaaactt atttttacaa atggcttctt 180
ttcacataaa ggattttgtga tggtttaatt ttgtgtgtca acctggctgg gccatagtgc 240
ccagatattg agtatatcat tgttctggaa gtttctatga aggtgatttt tggatgaaat 300
tatttaaatt ggtggacttt gagtaaagca gattatcctc catgatgtgg acagacctcc 360
cccatcantt gaaggaccgg gccaaaatga aaactgancc ctttgaggaa naaattctcc 420
aancanatgg cctttggtct gtttctctgg agaactgnga ctaatacagg ttcttc 476

<210> 466
<211> 218
<212> DNA
<213> Homo sapiens

<400> 466
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cctcanaagg ccagccaccc tcaanggagc aacccattgg ncccagactt ntcgcacgga 120
tgccagaaaa actttnaatt ggaaggaagg cttgaaggtc aacaatgggg naaanaagtt 180
ttttaaaaaa ataaaaaang gggagcctaa tattgtgg 218

<210> 467
<211> 82
<212> DNA
<213> Homo sapiens

<400> 467
cccgtgcatg gtggcttgtg cctatggacc cagctgctca agaggctgag gtgggaggac 60
tgcttgagcc caagaagtcc aa 82

<210> 468
<211> 90
<212> DNA
<213> Homo sapiens

<400> 468
cacttttggg agggccaaac aaagaangnn ttggttngac cccaggagtt tgaaaccaga 60
actggacaac atagtaaacc tcatccctac 90

<210> 469
<211> 262
<212> DNA
<213> Homo sapiens

<400> 469
ataataagat ccttgaaagc aggcctgaac caccattgta caataaacat ttcctgcatg 60
aataaattaa tgaaagaatg aataataaaa caagatctct tcccagagaa agtttaaagc 120
ctctgaagac agcagacatc catttgaata accacataac aaagtgaatc atttatattg 180
caaaagacag agaaagcatt atacttgagg gcagaggagg gagaaagcat attactcaaa 240
taaagatgtg atactgaatt ag 262

<210> 470
<211> 265
<212> DNA
<213> Homo sapiens

<400> 470
cngggnttgn naaatnngcc cgtgaancnc anatnaancn cggcccacan aancaatggt 60
aggaagcata accagagtga atcgattcct tgatcctgct ctgccaaaaa attaaagagg 120
agcactcctg gggtttttaa cccagataag acttcagcca cagccgtatt tcccatgttc 180
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gagttctgcc ggttcatctg gcttt 265

<210> 471
<211> 268
<212> DNA
<213> Homo sapiens

<400> 471
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atctttttct ttcatgcttg tccaacaaga gagcacattg ttagtgtgct tgaattccaa 180
caaaagaagg catagaatga atcttggttg ttccctttta cttgctaaat atgtactgaa 240
tgaataaatg gtgcattata catctatt 268

<210> 472
<211> 456
<212> DNA
<213> Homo sapiens

<400> 472
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tacctccact gtcttacact gtgaagagcg ggacaaaccg atgagtgaca gactactgaa 120
tcaatcccct tttaagctgc ttaagttcca gatttagttt taaagagaaa aaaaattgtc 180
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cagaggcgca atggggnctt tatactacca cctaaaggcn ggtnggatga ccatccctat 420
aactttgttt ttaattnaag acaaacatgt aattag 456

<210> 473
<211> 170
<212> DNA
<213> Homo sapiens

<400> 473
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ggcctttggag atagagccca gctttttcat tgcgcaggtg gaaaactgag gccagatgcc 120
gtgggacaga tgcagagaat gataaagtca ccaaatgacg gtgattattg 170

<210> 474
<211> 467
<212> DNA
<213> Homo sapiens

<400> 474
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gcgttcgcgg gnttgccant tttttaaggt ccaaccctgg cttgtttttg ggnnaaaaac 420
naaaccnaaa cccccaanga attggnctttt ngggtcattt ccttggg 467

<210> 475
<211> 440
<212> DNA
<213> Homo sapiens

<400> 475
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catctatgag taaaggagaa aaaaagaacg taaagacaaa atgcagctaa tactgaccaa 120
gacttacagg aacggtaaag ccctgtgatg aatgtcctgt tttttcctca ttcaaaagat 180
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ttgaccctct ctgagattca gttttttcat ctgtagaaat ggggacctaa ggtacagagt 360
ttcttctggg agaattaagt gaaactgcat gcaacaccat gttaggcaca ctagaagtga 420
tcaataaata ctacttgagt 440

<210> 476
<211> 438
<212> DNA
<213> Homo sapiens

<400> 476
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gcagtcactg gcccagacac agcgctggac acaacacccc ccgcttccca cagctgctga 180
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gtgtgcatcc tactctgctc acagtggagg catctttgga agaagtgact tattttctgg 360
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tcttacagaa attgcacc 438

<210> 477
<211> 193
<212> DNA
<213> Homo sapiens

<400> 477
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tctgccatgc cttccctgtc atcatccact cttgcagcac agctggccct ctgtatctgc 120
gggttccaca ccgatggatt caactgaccg tggatcagaa atacccagaa aaaaaattat 180
atctctactg aac 193

<210> 478
<211> 345
<212> DNA

<213> Homo sapiens

<400> 478
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tcttgcatgc cagcacagac caatggcaat ggatgtctga atcactgggt taacaaggaa 180
aagaatgctg tgcttaagta gcaatgtctg ctctgagcat ggcaggagaa attattggca 240
cctctgtcag atatttgata tctatttctt aaatagaata catacatatt ctaagaacaa 300
gaaaagcata aacaaattaa taaattactt tctgacttct aaacc 345

<210> 479
<211> 240
<212> DNA
<213> Homo sapiens

<400> 479
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ctgaccttta ccatcggtat aaccnactct ttacctccca aggctcgctc atttgtactt 180
attttttctc attgtctctc aaatttancc aactggnatg aataaactgg aagtaaacag 240

<210> 480
<211> 504
<212> DNA
<213> Homo sapiens

<400> 480
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ttctagaaac ccatgacttg acatcattgc gcggccacct gactcccagc tggcttcagc 120
ctctncgttt natctccctc tactctnact ctgctgctac caagtcagac ttnttttcan 180
aatgccctgt atcattttaa tgactggagt gtgactttgt tctcagcaca atgagtaaca 240
aagccaaaac actggagaat acgtttacgt attnaagaaa acctcagaca aggaagaatg 300
ctttcataat acagnacatt anaatcagac gaagcctnga agggcanaat naccgatcct 360
gaaaaatcan agtgtnctac agaagaagac gacagcgttt gagcacattt gttgaagcag 420
cctcctntcc cttatggnnc gataatccca caccgnttta ccatgctctc tggccttccc 480
agaacatcaa taaaaactgc atcc 504

<210> 481
<211> 274
<212> DNA
<213> Homo sapiens

<400> 481
taactggcag aacccacacc ttcaaaacag agactttggc tgcatctggc ctcctgctct 60
gtcttcctct cacctcctcc acctccatgt cacctactga gggatcgctt gagaacacca 120
gaatttcaga agacagagtt tgaacatcac tgacctttac catcggtata accaactctt 180
tacctcccaa ggctcgctca tttgtactta ttttttctca tgtctctcaa atttagccaa 240
ctggtatgaa taaactggaa gtaaacagtt ctac 274

<210> 482
<211> 299
<212> DNA
<213> Homo sapiens

<400> 482
gtaatcttct catctgtgag gatatggaac cccaacctct tcctggacac ctgatgatct 60
gcttgtgatg ggctcagagt cttgaaacac agaactatga gctcatctca tatcccaatc 120
cagcagcatg gaaacctcag actgtaaggc ccaagactgg cacttgttct ctcccaactc 180
ttttctttct ctctctcctt tcttttatcc cttaattcct tcttgcttcc ttccaagatt 240
tatactatta ccttttaggc aaaacatcct gaacatgtaa aataaactaa ttaaaatcg 299

<210> 483

<211> 395
<212> DNA
<213> Homo sapiens

<400> 483
gaggagtctg agaagaccta aaacagaaga gaaaaaggcg aagaagatgc ttaaatatat 60
acattattca agtaattaac tgaagccttg agcgtacaga tgatctccga aaggacgcca 120
cagaggggag aaggctggac ttgcagaaca cattgctgtt gaagaagtga caggaagatt 180
cagagctcac aaagaagaca ggtcagacgt ggagaggcga gccagcagaa caccctcaga 240
aatactgctc tcctgttcgg atggccagtt ttcatatttt agaatatttt tcaaaaagca 300
cttcaatata atgaagttcc ctcagttata acaaggccat ttttcatagc tatttgtgta 360
gatagtccaa aagtgtggtg tgttatcaga aaggg 395

<210> 484
<211> 440
<212> DNA
<213> Homo sapiens

<400> 484
gaagaaagca ttgctctgga aagagggaag ttcattcact catccaagaa gagcaaaggt 60
agatgccctg cggctatgga ggagggccgt ccaagctcac agttcctaga agtttgtgtc 120
accatttcac atttagcacc agaatccagc cttggcagat tcagggaagg aagccaagga 180
cacagctggt ggtgaagaca gaaactcctg tgtgacaact gccccctagg acacagttta 240
gggtcaatta acatttcctg aacaacttgc aaatggaaag agccatcccc aatgaagact 300
gaaaaatgag aggctcaact catctattat gacttgaacc caagtctatc tgtgtttgca 360
aaggctgtgc tgttgcacct agacctccac ccagaaacat gttttggggc tgacatttta 420
atagaaacat agagaggaaa 440

<210> 485
<211> 199
<212> DNA
<213> Homo sapiens

<400> 485
tcccgtctga actgttttgt cttggccctg tttccaccca ngaagccgca gatcctgact 60
ccttgtgttt gtttctctgc ccagatgaga aacacccatc acctctgact ttccaaggag 120
caaatcacgc tccgtgccgg gctcccccaa caacaccact ccctcttccc ttgcgatctc 180
caggnctcct ttgacactt 199

<210> 486
<211> 426
<212> DNA
<213> Homo sapiens

<400> 486
ctcncngctt taaatcctag ntggnngnac gggctgntna cctanaggct gtnntaggnn 60
cntcnnaacc acnccnagtt gcttcnagcc tccttngcgc cagcacatat ctgcanectt 120
gggccaccga tcctaagcca aagcctcccc aacctctggg ctcagaagca ggtgtaatcc 180
caactccagc agggaattcc agaggtgaag gtcacgggag catctttaat cttcggttcc 240
cagtagagaa gatacccaaa gagcagggag caggagccag ctccaggcta tacatttgtt 300
tattcatcaa tcattcattt atgcattaat cattcattcc ccccacccaa aaaaaaaang 360
gccagngngg ccaattcagn tngnacttaa ccaggctgaa nttgntnaaa ngggggggac 420
ccccaa 426

<210> 487
<211> 533
<212> DNA
<213> Homo sapiens

<400> 487
ttttttccc cccccccccg nggggggggn gnnnncnngg gggccccccc tctttttttgg 60
nggttcataa agggtggana cncccnttgg gcgccctttt tgggggggtt tnaaaaaaga 120

naaaatcctc ttcntggggc ccttaaaanc ccctcccctt ggaagataag gcnnnggggn 180
aacataacan ggggccgggg gcccccccca ctttatttgt ccccaagcct taaaattttt 240
ttttnggtaa ttttttttna aagnaaccaa anaanggggg gggggttttc cacccaatgg 300
gtttgggncc caaanaactn gggggtcctt ttggaaactt cccctgggga nccctcaagg 360
gngggaaccc caacttttggc ccttaaagcc cttnccccaa aaaggtggct tgggggggaat 420
tggcaagggt ggttggaaag tcaacccaca cccttggacc acaggtact aaataatttt 480
ggnccctttaa taaataagtn aaaaactggg atcatatgaa aatttaatat aag 533

<210> 488
<211> 473
<212> DNA
<213> Homo sapiens

<400> 488
agggaattac aatatnnctt tcnggnaagt ccgggccaga gaaaagggna cattgcctgg 60
gcttgccttt ggaaanganc cagggcaggg gaaaagcttc ttgggangga aaacccttgc 120
cgtcaagnaa ggcttgggan ggaaacttga aagaaagctt gttgttcttt ccgaagaaag 180
cttgaagctn accgggggcc aaagcttgcc aagtaagnaa tatccccttg ggatccaggg 240
gggggaaggg aaccacccat ttgttcggga ggaaagaata aggggaaacc aagccctttta 300
aacttgggga ttgaaaccaa gaaaaaatcc ttgcccnaaa ggggaagaag ggaaagcttg 360
aagcttgggg aaccgccttg ggaaccgaag aagttttgcc attttaagtt cccaagattt 420
accggggagg gnccgggccg cccgggctta nncaagtggg acccccaccg gtt 473

<210> 489
<211> 512
<212> DNA
<213> Homo sapiens

<400> 489
agcttaccct tggcntttta agnttcccct aacctntatn ggnggaaccc acctttattg 60
gantnnagta gantctccnt tgttgttntt tgaaaacccc anaaantttg gnaaaacnct 120
tttttctttt ttccttttggc ttttaaactt tttggccccc ccgggggttt tcccaanana 180
acagngnggc tttcaanccc cgaanggnaa tggnaatccn naagtttcca acaccacntt 240
gacttttccc angggaacnt caaaagccca agaagaangg ggcccaangg gacccaagct 300
tcgagggggac accacaagcc caggggggctt cttttccttc cgaaaacccc caaggggact 360
tgggactttg caaggggggt tggggacaag aaggttgggg ggttgggggg gggaaaaagc 420
aaattgcctt tgtcaaaccc acgttgggggg ggaaggcccca ctcccatttc ccaagggtgc 480
attaaaagtt tgaaggggaa acacctcctt gc 512

<210> 490
<211> 518
<212> DNA
<213> Homo sapiens

<400> 490
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tgtntgcttt ccggggccct ntggnggggng gggtnttgc caanncnttt ttggaaaaagg 120
gcccnaancc ccaacccaag ggggaacccn aaanacgttt ttccagnggc nttnggaata 180
aancttgaaa gggaagtttt gggaaaacac acttgggnan ggaacaaagg gcttcgggga 240
aagcntcaat cagccccgca ttcaaaacaa gaagtggaaa cttttcttgc caaagaatgc 300
cggggaagtt gggttttca agaagacatt ttcaagaaaa agtggaaagg ggaagaagac 360
tcaaaggatt tgactcatga agggaccttg aaaggggtg ggacatccca aggaaaaggg 420
gcctcttgaa aatttcccac acccaagcc gccttgttgc ttgagggact ccctccattg 480
ttgggcccca gggtggccac caaataaaaa aatcctac 518

<210> 491
<211> 344
<212> DNA
<213> Homo sapiens

<400> 491
acccatgcag gagacctctc caggtacaca tatttcctgc tactgaatgg cttagactgg 60

gatttgcaag gaactacgaa gtccaagacc tttgcctttc ttttagaaga aggcaccagc 120
tggttctcca atgttgaagg tcttctccag agatgaactc tgaaagccac atgttgagat 180
ggccccatta caggatggag agcacctgaa cccccaagtt atggactaga agaagacagt 240
tgccctggaa aatcatctga cccacattgg actttatgtg agggggaaat aaacctttat 300
tatgttaagc tacacaataa taaataacaa caataattgt gttt 344

<210> 492
<211> 381
<212> DNA
<213> Homo sapiens

<400> 492
tctccctgtc cttttnagtn cnccaaaact ngngggaaaa nctttnaaaa atatttctcc 60
cngggnaaaa tgnggnggaa aagtccntgg cacntgnaat gggccccctt tgtanggaaa 120
aaannaaccc caggggttcn tgggagttcc ncgaaccgtg gggnncnttg angggcncca 180
angggaagaa aaaaccnccg tggaaaccct taattaaagt tttngggggg tggaagaaga 240
agaaaaataa aaaccttaaa gtattgttaa agcttcttgt catttcaaag gggtaaatac 300
caagttgtgg gaaagggcaa gaaaaaaaat ggacccactc tccccttgga tatccattaa 360
aaaggatgtc ccaaaatcct c 381

<210> 493
<211> 639
<212> DNA
<213> Homo sapiens

<400> 493
tctgggggag cctaccttgc tttaacttcc tnaacttaaa ggtanaacaa cnccctnttt 60
tnccntgaaa aacnanggcn tttttngaca ttaaagncnc ttttaaggag gtatgcccaa 120
aaaaaggnaa ncccaacccc ttnngccaaa aaatnaaacn tcaaagangg ggcnggcnaa 180
antcngggaa ncntttnccc cagggggggaa gaagaatgaa cncttttttta ntggggcttt 240
ncagaaaaag gtggnaaggt ccacttggct ttttggcttg gnctttggga atcaaaggaa 300
ccnagaaaaa ggaaaattan ttggataccc aatggggaag ccttggaaga atgccatttt 360
ggtttgggga agggtttttc ttgtcttcaa acttgggtct cttgacaaag cctcttgact 420
tggaatggta ttcccgtggc ttgggccact tatgccaagc aaggcatcat taaatttaag 480
acggggactt ggcttgcacc tttccttgaa gaaagccaag actttccact tggatgggaa 540
agaagcttga aaaaaccacc aaagcccagg gaagtggcaa gaaccacttg gnccttaatt 600
tgcttncttg aagaattncc attattaata aaaagaaaa 639

<210> 494
<211> 342
<212> DNA
<213> Homo sapiens

<400> 494
ntagcctcag gatggaggtg gctgccagaa agaccaagta atgatcagaa gcatggaact 60
ttcagaccta ttcctcccaa cttctggaga gggngagtgc ctggagactg agttaataat 120
tgatcacgtc tacatgatga aacctctaag tgacaaggat cagagagctt ccaagttggt 180
gaatacatcc atgtgcaggg agggtggcct accctaaccc catcggacag gagcacccat 240
gttcaggaat cttctggacc tcaccttatg tattaatctc tctttatctg gctgttcatc 300
tatattcttc atagtatcct ttataataaa caagcaaatg tc 342

<210> 495
<211> 613
<212> DNA
<213> Homo sapiens

<400> 495
ntcntgaaac tggagttcgg ggtngtncna ttaattgggg aaatgggann ggggaaaaat 60
aaaaatggaa ctgggaatgg gngccgcttn cttttttttaa agntttcaaa aaatgaccat 120
ttnccaaaaa caaagcccgg gggccttgga ncccccgggc cttggttttt aaaaaatttt 180
aacaaacanc aagttccttg ggggaaaggg ngggggaacc cacccaacct ttttctttga 240
aataaacttg gggaagaat gaaaaacaag ggaaagcttc ttattgaaca ccactttgga 300

atcggaaata ttgaacaaga acacccggaa aaaatcaacg aacttcaagc ccccttccaa 360
gccaccttct tgccttgttt gccccgcccg aatcacaagc ccgggaatgg caagcttgaa 420
aaagaattcc cttgggggcc cttgggntcc caaacccgcc cacttgtggg actcttgaag 480
gccctcttgc atttgtgggg tggggtcttg ccttgtggat aatttttggg tcattggggc 540
ttgggtcttg gtccgggntt ncccatnttg gtcttggccc aaggctctat ggtnggcttn 600
aaatcccttt ggc 613

<210> 496
<211> 611
<212> DNA
<213> Homo sapiens

<400> 496
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tttttcaggg agccctttatg aaacaaaacc ccgggggttgn gttanggnta ctngggctng 120
ngtcccaccc nactgggttc ttttttttct tnttggggcc ccanaaatgg aaggggggatt 180
gccccaccaa ngggaccccc tttccaacca gaaccccnngg gacttattat taaaccctnt 240
tttttgcgcc cnaccattga atgggacttt gnaacccgca aaagcttgaa ggnccattcg 300
gatacgccc taacccctta ccccccggga acaatctttc attgggaaaa acaagccggg 360
ntttttttcc gacttttttac aaagccttcc cggtngggct tgggaaggcc attcttaagc 420
ttggcaagaa aaacaagcaa gggaaaggat gctttccggg ggaagcccct gatgccttga 480
aaaatgaaaa aaattantct taaaggctat tcaaatatca agccaagcca ttttttttcca 540
nggagaaang gaaaaaaggc cgaanaaaaa aacaaatttt ccaanaatgg ggttgncttc 600
cttccaaccc a 611

<210> 497
<211> 436
<212> DNA
<213> Homo sapiens

<400> 497
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actgatgtta gctttaaaag taaggagttc agagtgctct gtgctgaaca tctttcggtg 120
taattaagcc ttcatattcc tgaggaggag ctactaagac accctaccaa gtcctgggct 180
gtgcctggag gttagaaaac gaaccacata gtcctgtaat gacagaaaaa aattgaaaac 240
tgtatttttaa aaatgatttc tcaacaagac cagccggcca ctcaaccact tcagtacctc 300
gtttctggat gaagaccctg agcaggggat ttgcactaga aaccgccttg cagaagttgt 360
catcattgtt gatgggcagc aggtctccgt gcacatctgc atagccaata gttacatcac 420
tgttggagat atggtg 436

<210> 498
<211> 445
<212> DNA
<213> Homo sapiens

<400> 498
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tnaagtggan atngcngcca cctattatnc cnngatatat ttggtatacn aacnaagaaa 120
ctnaatnatn aattngacna tnaattttaa gggaaaaggn aaaagnaaac nccagggggc 180
cgggtggcaa tttgntttcc nttcttagtc ccttcaaaaa agtagaaaat agtgganatg 240
aagcagggtt gatatgaatt tggcttgctt ccccccccaa tcttaccttt gcttgnaggt 300
nccataatcc ccacatgtgg ggggaggaag cctttaggag gtgatttaat catggggtgg 360
gtacccgcat gctgtctcat gataatgagt gagttctcca agaattaacg cttttatagg 420
aacctttttc ccctttttact tggcc 445

<210> 499
<211> 295
<212> DNA
<213> Homo sapiens

<400> 499
gttcttccca ttctggagta anaggatgtt gcnttnnaag ggtngtggga agggnncnan 60

aancttnccn ggantaangg cctaagggng gctttngacc aagggaccct ccaagtcaag 120
gttcctttta catcacatat tgggaccccc aacagctggg cttcttcaag gtgagacaag 180
acctgtggtt tgaatccacc atttaatggc tgngtgatca tgtgcaactt actcaacctc 240
tcagagcctc aagtttcctc attaataaag tggagataat aatagaacac acctt 295

<210> 500
<211> 181
<212> DNA
<213> Homo sapiens

<400> 500
ggtttcctgg agttnggatt ttgctgactg cacactcacg gtgctatcca acatgancat 60
cttccctgca gtttctacaa tttggcagtt ggatccacct gaatcctttg gcaaggccaa 120
acgtggtgtc tnangaagaa cacattgaag tctctgtttt ttaaatatca ttatgacctt 180
g 181

<210> 501
<211> 469
<212> DNA
<213> Homo sapiens

<400> 501
cagaaactga gatgaaagct ggggttggag atggagtttg tcattttntg ancttaaann 60
naccngcntn ataacaaaag ccagcncacc ccanacngga gaatggaaag ggaggaaaaa 120
tttgggtccc gtcttttaca agggntgntg agttacttca ccaatcctgg aatgctgatc 180
ttttgggaac ttgttaaaca gtctttccac cccctttgtt cgaagctttt ggtgaagtgt 240
ttcanaaact gacgaaatgc aggatcgttt tccttacaca cacaaatgcc atggcaacag 300
caacttcgtg acaacagcaa agaaagccag actgggaatt tgccaaccca gagtggtgac 360
catctgtgag ggcccaaacc cttcaaatgt tgccccgttc taaagtgctt atcttaaccc 420
angcttttgt acatagcaaa agcgacattt aaagtgacat aagaatggg 469

<210> 502
<211> 400
<212> DNA
<213> Homo sapiens

<400> 502
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cntttttttg ccttgggaac gacccatttg ggggggaaan ttaaaacccc ccccttnttt 120
ggcnncnttg tntgnaaaag naaattggcc ccccggggcc cttttttttnc ccctttgggc 180
caaaggggaa ttttttaaac cctttaaaaa attgggtntt ggccttgggg gaacctttgg 240
cccaagaatg ggccccaaaa agngggnacc cccaataact nttancccccc tntttggcct 300
tggttcaagc ncccaaaagg naaaanaaga ccctggngtc nntttggggg aggtggggng 360
gaaacccaaa atcccatttn gggggntttt ttttaaacct 400

<210> 503
<211> 185
<212> DNA
<213> Homo sapiens

<400> 503
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ggagccccna atggaactta aaaatttctt gttggggggt tggggaggaa gaataaaaaa 120
tgccccccttt nttnggggcc cttggacccc ttattttggc cccttgccca ttgcttgggc 180
ccttg 185